OPHTHALMIC DEVICES PANEL EXECUTIVE SUMMARY

RESURE® SEALANT

INDICATION FOR USE: RESURE® SEALANT IS INDICATED FOR INTRAOPERATIVE MANAGEMENT OF CLEAR CORNEAL INCISIONS WITH A WOUND LEAK DEMONSTRATED BY A SEIDEL TEST, AND FOR PREVENTION OF POSTOPERATIVE FLUID EGRESS FOLLOWING CATARACT OR INTRAOCULAR LENS PLACEMENT SURGERY.

PMA# P130004

ADVISORY COMMITTEE MEETING DATE: SEPTEMBER 19, 2013

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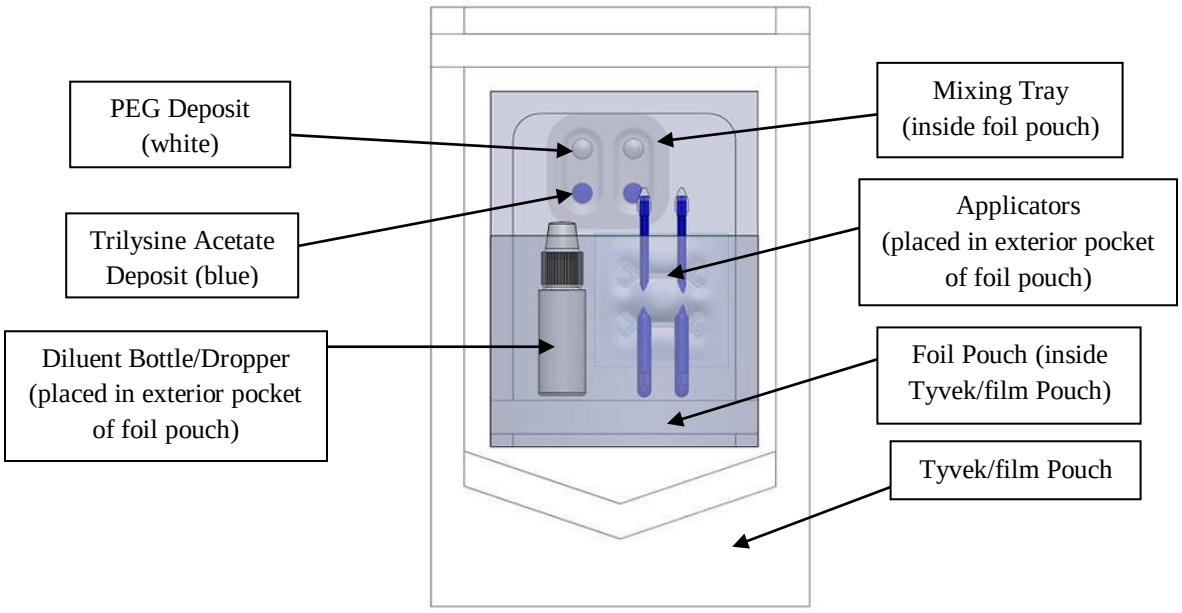
1.0 EXECUTIVE OVERVIEW

Ocular Therapeutix, Inc. (OTX) is a small healthcare products manufacturer specifically focused on developing medical devices, such as ReSure® Sealant, and drug delivery products utilizing a proprietary polyethylene glycol (PEG) hydrogel technology to address unmet and underserved needs in ophthalmology. ReSure Sealant is an *in situ* formed PEG hydrogel that is applied topically to clear corneal incisions to create an adherent temporary, soft and lubricious sealant. The chemical composition of ReSure Sealant is equivalent to another Ocular Therapeutix product, ReSure Adherent Ocular Bandage, which is commercially approved in Europe and Australia. ReSure Sealant and ReSure Adherent Ocular Bandage use the same proprietary PEG hydrogel technology used in DuraSeal Dural Sealant (Confluent Surgical, Inc.), approved by the Food and Drug Administration (FDA) on April 7, 2005 under Premarket Approval Application (PMA) P040034 and DuraSeal Spinal Sealant (Confluent Surgical, Inc.), approved by FDA on September 4, 2009 under PMA P080013. Confluent Surgical and Ocular Therapeutix have the same technology founder, Amar Sawhney, Ph.D.

Following Pre-Investigational Device Exemption (Pre-IDE) negotiations with FDA, Ocular Therapeutix chose to pursue FDA approval of its PEG hydrogel technology for a first of a kind ocular sealing indication. ReSure Sealant, the subject of this PMA (P130004) application, is a topical liquid hydrogel that creates a temporary, adherent, soft and lubricious sealant for intraoperative management of clear corneal incisions to prevent postoperative fluid egress following cataract or intraocular lens placement surgery. ReSure hydrogel is completely synthetic, with no animal or human derived components. The main components of ReSure hydrogel are water and PEG, which have a long history of safe use in medical devices, pharmaceuticals and cosmetic products including ophthalmic products. The formed hydrogel has been designed with a modulus of elasticity slightly softer than contact lens hydrogels. **Figure 1** provides an illustration of the ReSure Sealant device.

Figure 1: ReSure Sealant Packaging and Components



Under an IDE approved by FDA, ReSure Sealant was evaluated in a prospective 488 subject pivotal trial in which the hydrogel sealant was compared with suture(s) to prevent incision leakage from clear corneal incisions. This evaluation demonstrated that ReSure Sealant was not only non-inferior, but also superior to suture(s) for the prevention of incision leak while also evidencing a favorable safety profile. As both safety and effectiveness of the subject device were demonstrated, the ReSure Sealant Pivotal Study results presented in PMA P130004 support FDA approval of the device for the proposed indication for use, namely: ReSure® Sealant is indicated for intraoperative management of clear corneal incisions with a wound leak demonstrated by a Seidel test, and for prevention of postoperative fluid egress following cataract or intraocular lens placement surgery.

1.1 Background

Treatment of cataracts has become one of the most prevalent surgical procedures with approximately 3.2 million cataract/lens implant operations performed in the United States annually[1]. The majority of surgeons in the U.S. now routinely perform their cataract surgery using smaller clear corneal incisions (CCIs).[2] The stability of CCIs in the early postoperative period has come into question.[3,4,5,6,7,8,9] Studies have demonstrated that incision integrity is lost when intraocular pressure (IOP) fluctuates or during the application of external pressures or patient manipulation.

If wound integrity is suspect, the only current treatment option for definitive closure is sutures. Although stromal hydration is frequently used to mitigate potential wound leakage, the stability of incisions treated with stromal hydration has been questioned based upon reports of epithelial gaping [(3,10)] and leak rates of 50-85% in the immediate post-operative period.[8,11,12] Sutures are considered the current gold standard for ensuring closure of CCIs, but they are not ideal. Sutures can result in poorly apposed wounds,[13] can cause tissue damage, and histological imaging has demonstrated they can cause vacuole formation in the corneal epithelium.[14] It is recommended that sutures be removed promptly once healing is complete to decrease the chances of infection.[15,16] This requires additional post-operative visits, which may be inconvenient for the patient and time-consuming for the surgeon.

Surgeons often test the incision site for leakage with simple digital pressure, but this technique is variable and is likely to provide only a gross indication of wound integrity. A preferred technique would be a wound challenge that is standardized, quantifiable, and reproducible. A recent study with a Calibrated Force Gauge manufactured by Ocular Therapeutix showed that one ounce force applied to the eye in healthy volunteers could raise average IOP by about 25.95 mm Hg, consistent with levels noted in forced blinking or eye touching. That level of force was sufficient to cause wound leakage in 67% of the eyes which were sealed using stromal hydration alone, and 24% of eyes sealed with stromal hydration and a suture. Such a gauge represents a consistent and reproducible provocative test to challenge wound integrity for wound leakage post-surgery.[12]

Although sutures are currently the most effective option for closing clear corneal incisions, there is often a reluctance to use a suture due to the concerns that suture complications may ensue. For this reason, ReSure Sealant represents a novel technology that addresses deficiencies in observed wound sealing by providing an alternative to sutures for definitive wound closure.

1.2 Clinical Study

The ReSure Sealant Pivotal Study was designed as a prospective, randomized, parallel-arm, controlled multicenter, subject-masked study to evaluate the safety and effectiveness of ReSure Sealant compared to 10-0 nylon suture(s) to prevent incision leakage from clear corneal incisions in subjects undergoing uneventful clear corneal cataract surgery. Patients scheduled for routine cataract surgery, with no confounding ocular pathologies were recruited for this study. Single-plane clear corneal incisions less than or equal to 3.5 mm were included in the study. For the purpose of this study protocol a single plane incision was defined as an incision that extended into the corneal stroma then was angled down toward the anterior capsule of the lens. The study evaluated 488 subjects and involved 24 investigational sites within the United States. Subjects were randomized in a 5:3 schema to receive ReSure Sealant or sutures. A suture was selected as the comparator device for this study as it is generally considered the "gold standard" closure method for treatment of incisional leaks.

If surgery was uneventful, eligible subjects were tested using a Wound Leak Assessment as follows. A Seidel test was conducted on the main clear corneal incision of the eye. If there was spontaneous leakage, it was noted. If not, a Calibrated Force Gauge (CFG) was used near the incision to apply force to the cornea (in 0.25 ounce force increments, up to 1 ounce force). Force was discontinued if leakage was observed. The eye was monitored for leakage using a Seidel test. Those eyes with unprovoked leakage or leakage under the Wound Leak Assessment were randomized to the treatment (ReSure Sealant) or control (suture) group. Those eyes that exhibited no unprovoked leakage and no leakage at 1 ounce force from the CFG application were considered screening failures and were excluded from the study. Subjects were masked as much as possible to their treatment. A post-study masking assessment was conducted.

After the initial wound leak challenge, subjects were randomized to the sealant or suture. After incision treatment a second wound leak assessment using the CFG was conducted. Any leakage at this point was considered a primary endpoint failure. These subjects were treated for leakage at the surgeon's discretion using their standard technique; further application of the ReSure Sealant was not permitted. Subjects were evaluated at 1 hour, 1, 3, 7 14, 21 and 28 days after surgery. A standard Seidel test was performed on days 1, 3, 7 and 28. The primary effectiveness endpoint was the proportion of eyes with any wound leakage within the first 7 days of surgery. Subjects were exited from the study at Day 28, provided ReSure Sealant was no longer evident on the cornea.

Routine follow-up was conducted, including vision testing, IOP measurement using applanation tonometry, slit lamp evaluation, corneal topography and keratometry. Secondary endpoints included best corrected visual acuity (BCVA) differences in groups at Days 1 and 28, and surgically-induced astigmatism differences at Day 28. Subjects were also asked to complete the Ocular Comfort Index (OCI) daily for the first week after surgery and at the Day 14, 21 and 28 visits.[17] Safety endpoints included the degree of corneal edema and anterior chamber inflammation at Day 1. Adverse events were also recorded.

A total of 583 subjects were consented (enrolled) and screened for potential participation. The study randomized 488 subjects. It is noted that 487 unique study subjects participated in the study as 1 study participant was consented twice, was assigned two different subject numbers, and had both eyes

randomized and treated by ReSure Sealant. The data for both eyes was included in the safety analysis, but only the data from the first enrolled eye was included in the primary efficacy analysis.

Of the 488 subjects, only 6 did not complete the study, representing a high subject retention rate of 98.8%.

The basic demographics of the study population are presented in **Table 1**. The subjects included in the two treatment groups were similar with respect to demographics as there were no statistical differences among the variables evaluated.

Table 1: Subject Demographics

Variable	ReSure Sealant (N=305)	Suture (N=183)
Age (years)		
Mean	68.80	68.84
Median	69.08	69.08
SD	8.93	8.55
Min. – Max.	31.9-91.0	43.8-91.4
Gender, n (%)		
Female	167 (54.8)	107 (58.5)
Male	138 (45.2)	76 (41.5)
Race, n (%)		
White (Caucasian)	279 (91.5)	169 (92.3)
American Indian or Alaska Native	0 (0.0)	0 (0.0)
Asian	5 (1.6)	1 (0.5)
Black or African American	12 (3.9)	9 (4.9)
Other	9 (3.0)	4 (2.2)

1.2.1 Effectiveness Evaluations

The primary effectiveness endpoint was clear corneal incision leakage manifested with a positive Seidel test indicating fluid egress at any time between the immediate post-operative period and up through 7 days. The primary effectiveness endpoint event rate was 4.1% for subjects treated with ReSure Sealant compared to 34.1% for subjects who had their incisions sutured ($p<0.0001$). Within both treatment groups the majority of leaks were in the immediate post-operative period. For ReSure treated eyes, of the 12 endpoint event leaks, 11 occurred in the immediate post-op period and 1 occurred at Day 3. For sutured eyes, of the 60 endpoint event leaks, 58 occurred in the immediate post-op period and 2 occurred at Day 7. There were no wound leaks in either treatment group beyond the Day 7 visit.

ReSure Sealant was statistically non-inferior to sutures for prevention of clear corneal incision leakage. Furthermore, clear corneal incision leakage occurred significantly less for subjects treated with ReSure Sealant, demonstrating that ReSure Sealant is more effective than sutures for mitigating clear corneal incision leakage ($p<0.0001$). The wound leak rates for both the ReSure group and the Suture group were

significantly less than the leak rate of 67% reported by Masket *et al*. for clear corneal cataract incisions closed with stromal hydration alone.[12]

Upon FDA request a post hoc primary effectiveness analysis was performed stratified by subject gender and age categories. The leak rate was demonstrated to be substantially lower for ReSure Sealant compared to suture in all evaluated subgroups including males, females, and age groups stratified in increments of 10 years from 60 years and beyond. Within the category of octogenarians (≥ 80 years) there were less wound leaks in the ReSure Sealant group, but the sample size within this strata (n=40) was too small to demonstrate a statistically significant reduction in post-operative wound leak rates relative to suture.

There were no statistical differences between treatment groups for any of the secondary effectiveness endpoint parameters evaluated: (1) surgically induced corneal astigmatism at Day 28, (2) BCVA worse than 20/40 at Day 1, or (3) BCVA worse than 20/40 at Day 28. These secondary effectiveness endpoints were pre-specified in the protocol for potential inclusion in the labeling on the chance that the results favored the ReSure Sealant. However, the study was not powered for these endpoints or inherently designed to investigate these secondary parameters as doing so would have required additional rigorous controls over the variables that may impact these analyses adding complexity to the study while adding no value to assessment of the primary endpoint.

The presence of ReSure Sealant can be characterized as 1 to 3 days, which corresponds with the period of epithelial healing. The hydrogel sealant was not observed to be present in visits beyond the Day 7 visit. The observed persistence of ReSure Sealant is clinically relevant in that it covers the clear corneal cataract incision for the early postoperative days while the epithelium is healing, which is the period that incisions are most vulnerable to leakage.

The proportion of responses for "Very Easy" to use was slightly higher for ReSure Sealant (54.8% vs. 41.0%) indicating that ReSure Sealant is at least as easy to apply as sutures.

1.2.2 Safety Evaluations

Safety of ReSure Sealant was assessed through spontaneously reported adverse ocular events, as well as through thorough ophthalmic examinations including a slit lamp examination, BCVA, keratometry/topography, tonometry, assessment of ocular irritation via the OCI, wound leak and wound healing.

The overall incidence of adverse ocular events (AEs) reported for subjects treated with ReSure Sealant was significantly lower than for subjects treated with suture (22.7% vs. 45.4%, $p<0.0001$). This difference in adverse ocular event rate between the two groups is attributed primarily to the higher incidence of device-related adverse events in the Suture group. Within the ReSure group the percentage of subjects experiencing device-related AEs was significantly lower than for the Suture group (1.6% vs. 30.6%, $p<0.0001$). Excluding the adverse ocular events for subjects in the Suture group that were device related or with "unable to determine" relationship (i.e., the events of subconjunctival hemorrhage, eye irritation, eye pain and others), there is no difference in between the ReSure group (22.7%) and Suture group (21.9%) for the remaining events (*post hoc* analysis; Fisher's Exact Test; $p=0.9107$).

Within both treatment groups, the majority of AEs were mild in severity. The incidence of any major or serious adverse ocular events was very low and did not differ between the two groups 1.6% vs. 0.5% respectively (p=0.4173). The percentages of subjects experiencing severe adverse ocular events were comparable between the two groups; 0.7% for the ReSure group and 0.5% for the Suture group. There were no severe device-related events or any unanticipated adverse device effects noted for either treatment group.

Three (3) subjects (1.0%) treated in the ReSure group experienced a serious adverse event (SAE) including 1 event each of non-proliferative diabetic retinopathy with cystoids macular edema (CME), Descemet's membrane detachment and acute post-operative inflammation. None of the serious adverse ocular events were determined by the Investigator to be device-related. The nature of these serious adverse ocular events reported is consistent with a patient population undergoing phacoemulsification for cataract extraction with intraocular lens (IOL) placement. In both treatment groups the rates of adverse ocular events addressed in either the "FDA grid" or International Organization for Standardization (ISO) 11979-7 "Ophthalmic implants — Intraocular lenses —Part 7: Clinical Investigations Amendment 1" for subjects undergoing posterior chamber IOL placement were within the threshold rates cited in these documents.

There were no statistically significant differences between the two groups for the endpoints that had been established *a priori* for potential inclusion in the product labeling: 1) incidence of corneal edema (moderate to severe stromal edema) at Day 1 or 2) ≥ grade 2+ anterior chamber inflammation at Day 1.

1.2.3 Conclusions

ReSure Sealant has been demonstrated to be clinically and statistically effective in the prevention of clear corneal incision leakage. Safety of ReSure Sealant when applied to clear corneal cataract incisions has also been established as there was a lower incidence of adverse events, as well as a lower incidence of device-related adverse events associated with ReSure Sealant than there were with sutures. The adverse event profile observed was favorable in a patient population undergoing cataract surgery. There were no unexpected findings associated with the use of ReSure Sealant.

The device provides improved benefit over the current available alternatives with no substantial risk. The probability of patients experiencing benefit is very high as the device was demonstrated to be superior to suture, which is regarded as the "gold-standard" for definitive treatment of incisional leaks. The potential frequency of harmful events associated with the device is very low and is significantly lower than for sutures. The nature of these events is not serious and is consistent with a patient population undergoing phacoemulsification with cataract extraction and IOL placement. Therefore, it is reasonable to conclude that the benefits of use of ReSure Sealant outweigh the risk of injury when used as indicated in accordance with the instructions for use.

Results from the ReSure Sealant Pivotal Study provide valid scientific evidence to establish that ReSure Sealant is safe and effective for intraoperative management of clear corneal incisions with a wound leak demonstrated by Seidel test, and for prevention of postoperative fluid egress following cataract or intraocular lens placement surgery.

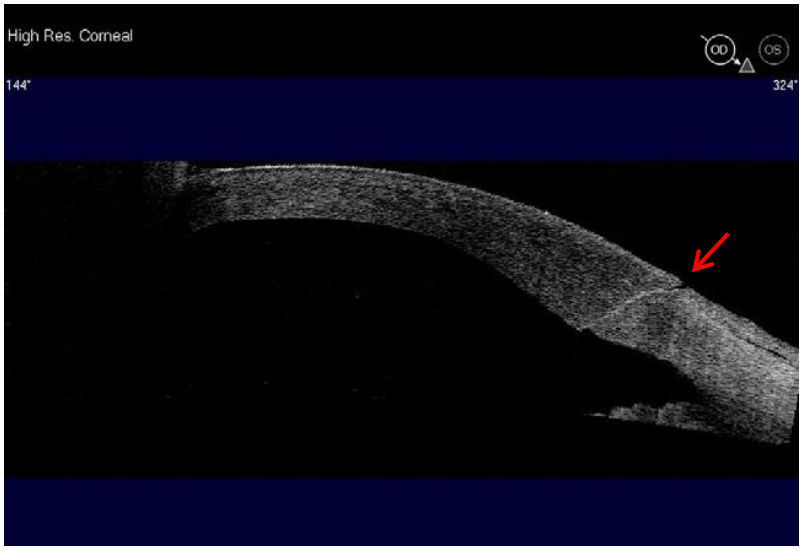
2.0 INTRODUCTION

Cataracts affect nearly 20.5 million Americans age 40 and older. By age 80, more than half of all Americans have cataracts. This ocular condition is the leading cause of visual impairment as well as the leading cause of blindness in the United States.[18,19] Due to changes in population structure and increased life expectancy, treatment of this condition has become one of the most prevalent surgical procedures. It has been estimated that approximately 3.2 million cataract/lens implant operations are performed in the United States annually.[1]

The complementary developments of phaco-emulsification for surgery and foldable IOLs for implantation have driven the evolution of modern cataract surgery. These two factors mean incisions can be smaller with potentially faster healing and lower levels of surgically induced astigmatism. As incisions have dropped in size, surgeons have migrated from the sclera to the cornea; the majority of surgeons in the U.S. now routinely perform their cataract surgery using smaller (i.e., typically < 3.5 mm in width) clear corneal incisions (CCIs).[2] While CCIs are often considered as self-sealing, their integrity especially in the early postoperative period has been questioned.[3, 4, 5, 6, 7, 8, 9]

Studies have demonstrated that incision integrity is lost when IOP fluctuates or during the application of external pressures or manipulation. Reports in the literature demonstrate IOP levels may be low in the immediate postoperative period with one study reporting 20.5% of patients had an IOP ≤ 5 mmHg 30 minutes after clear corneal cataract surgery.[20] Using optical coherence tomography (OCT), epithelial gaping (see **Figure 2**) has been observed in 9-12% of the wounds at postoperative day 1 demonstrating that stromal hydration (if used) is not always sufficient for assuring a water-tight incisional closure.[3,10]

Figure 2: High-resolution OCT image showing gaping (red arrow) at the epithelial side of the CCI[10]



This is of particular concern as an incompetent wound allows for the transfer of fluid into or out of the incision and thus presents the potential for inoculation of the aqueous humor with infectious agents from the patient's ocular surface or adnexa.[9] Indeed, in meta-analyses, suture-less incisions have been

implicated in the rise of post-operative infections following cataract surgery. In a systematic review of the literature, Taban *et al*. found a higher rate of endophthalmitis after use of clear corneal incisions compared with scleral tunnel incisions, 0.19 and 0.06–0.07%, respectively.[21] For this reason, a range of prophylactic measures have been instituted in the performance of CCI cataract surgery, including the routine use of prophylactic peri-operative antibiotics.

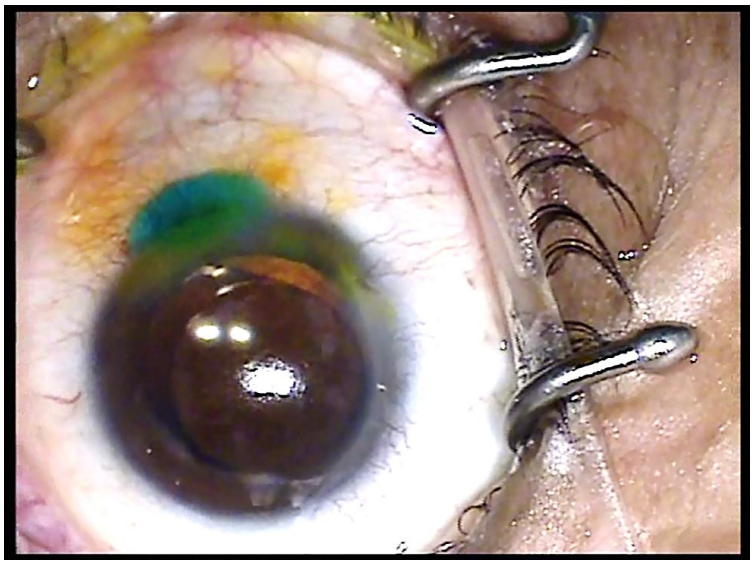
Seidel testing for wound integrity and leaking is not routinely performed and wound leakage has not been systemically evaluated in a large study. Of the few studies prospectively evaluating leakage of the main cataract incision, one observed an immediate post-operative leak rate of 85% following application of conventional stromal hydration[11] and another reported a leak rate of 12% (12/100) on post-operative day 1.[22] In an attempt to better evaluate incision integrity, several studies have challenged clear corneal incisions following cataract surgery. One study used an irrigation cannula to simulate external pressure and reported a leak rate of 50% (4/8).[8] Another series of studies incorporating an intra-operative wound challenge using the same Calibrated Force Gauge and methodolgy used in the ReSure Sealant Pivotal Study demonstrated a wound leak rate of 67% (20/30) for main incisions closed with stromal hydration and 24% (5/21) for those closed with suture.[12]

Despite the numerous technological advancements that have been made in the development of equipment and procedures for cataract surgery, there has been little in the way of progress or new technologies available for providing definitive closure of incisional leaks. If wound integrity is suspect, the only current treatment option for definitive closure is sutures. Although stromal hydration is frequently used, the stability of incisions treated with stromal hydration has been come into question based on reports of epithelial gaping[3,10] and leak rates of 50-85% in the immediately post-operative period. [8,11,12] Sutures are considered the current gold standard for ensuring closure of CCIs, but they are not ideal. Sutures can result in poorly apposed wounds,[13] can cause tissue damage, and histological imaging has demonstrated they can cause vacuole formation in the corneal epithelium.[14] Sutures provide a relatively weak resistance to wound leakage, similar to fibrin adhesives;[23] 23.8% of sutured CCIs showed leakage after application of one ounce force.[12] Studies comparing sutureless and sutured CCIs have produced conflicting results with regard to their overall effect; different India ink inflow patterns have been observed in different studies.[7,13] It is recommended that sutures be removed promptly once healing is complete to decrease the chances of infection.[15,16] This requires additional post-operative visits, which may be inconvenient for the patient and time-consuming for the surgeon.

ReSure Sealant, the device presented in this PMA P130004, is a proprietary *in situ* formed hydrogel consisting primarily of water (approximately 89%) and polyethylene glycol (approximately 9%), a material with a well-established history of safe use in ophthalmic products. Unlike sutures, ReSure hydrogel is easy to apply and provides a temporary absorbable, soft and lubricious surface barrier requiring no secondary removal procedure (**Figure 3**). It is designed for intraoperative management of clear corneal incisions with a wound leak demonstrated by Seidel test and to prevent postoperative fluid egress following cataract or intraocular lens placement surgery. ReSure Sealant may be used alone or in conjunction with stromal hydration. The hydrogel material selectively adheres to de-epithelialized tissue during the post surgical healing process providing coverage when the wound is most vulnerable (1-3 days). ReSure Sealant can intercalate with the surface irregularities of the epithelial defect. As re-epithelialization occurs, hydrolysis of ReSure Sealant is taking place and the material sloughs off in the

tears. Since all epithelial defects are not identical, some variation in sealant persistence is expected, as the rate of healing and closing of the defect will vary from patient to patient. The observed persistence of ReSure Sealant which was demonstrated to range primarily from the first to the third post-operative day is clinically relevant in that it covers the clear corneal cataract incision for the early post-operative days while the epithelium is healing.

Figure 3: Image of ReSure Sealant Immediately After Application



Recognizing that the highest degree of wound integrity is an important goal in cataract surgery procedures, ReSure Sealant will provide ophthalmic surgeons with a valuable tool and an alternative to sutures for providing safe and effective closure of a clear corneal incision.

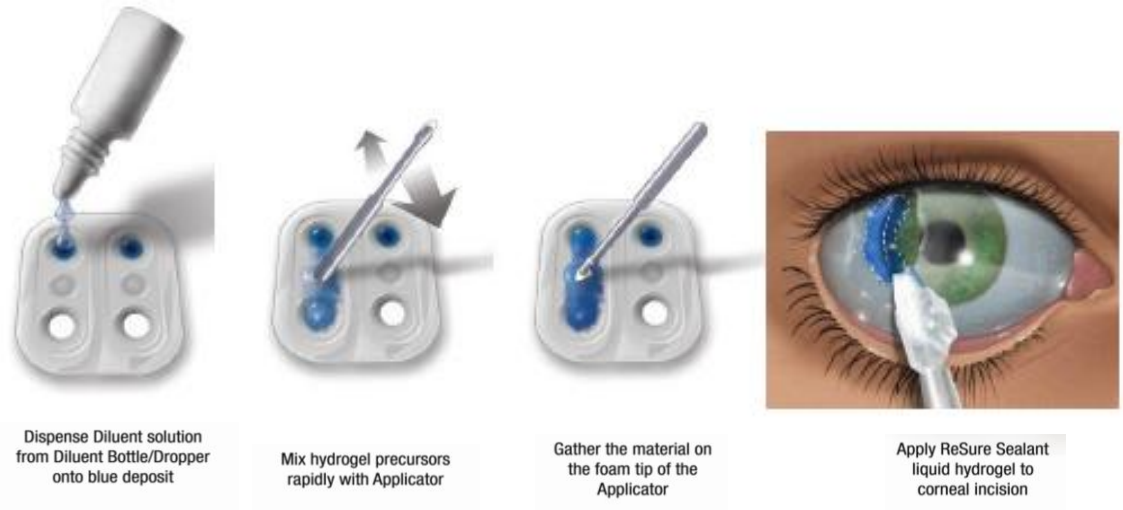
3.0 RESURE SEALANT

3.1 Device Description

ReSure Sealant is provided in a single use package with all necessary components. The device configuration consists of one plastic bottle/dropper combination filled with diluent solution, a mixing tray with two mixing wells containing lyophilized deposits of reactants (one blue deposit and one white deposit), and two Applicators. The mixing tray is packaged within a foil pouch that has an exterior pocket where the diluent bottle/dropper and Applicators are placed. The sealed foil pouch is then placed in a Tyvek/film pouch. The sealed Tyvek/film pouch provides the sterile barrier. The plastic bottle/dropper is used to dispense two drops of the diluent solution on the trilysine acetate deposit (blue deposit). The trilysine acetate deposit contains a blue visualization aid to facilitate hydrogel application to the incision. The Applicator is used to mix the reconstituted trilysine acetate deposit with the PEG deposit (white deposit) within the tray mixing well to initiate a crosslinking reaction to form a biocompatible, absorbable hydrogel. ReSure Sealant is applied to the corneal incision as a liquid using the atraumatic foam-tipped Applicator.

The Applicator applies a conformal coating that adheres to the ocular tissue. The applied liquid solidifies within approximately 20 seconds into a soft, pliable hydrogel that remains on the corneal surface for up to approximately 7 days. Unlike cyanoacrylite glue, ReSure hydrogel is soft with a modulus that represents natural tissue, similar to a contact lens bandage. ReSure Sealant's adherence to tissue is mechanical in nature. As an *in-situ* forming hydrogel, it contacts the tissue surface as a liquid and fills the surface irregularities of de-epithelialized tissue. Surfaces where the mucosal and epithelial tissue are intact, present a liquid mucous surface, which does not enable firm adherence. Adherence to de-epithelialized tissue is much firmer, since the mucous layer is not present, and ReSure hydrogel can intercalate with the surface irregularities of the epithelial defect. As re-epithelialization occurs, the ReSure Sealant hydrogel softens, detaches and is sloughed off in the tears as the epithelial defect closes. Two applications per ReSure Sealant device are provided in the event a procedural delay results in solidification of the material before application or the surgeon perceives the need for additional material to properly cover the incision.

Figure 4: ReSure Sealant Application Process



3.2 Proposed Indication for Use

ReSure® Sealant is indicated for intraoperative management of clear corneal incisions with a wound leak demonstrated by a Seidel test, and for prevention of postoperative fluid egress following cataract or intraocular lens placement surgery.

4.0 SUMMARY OF NONCLINICAL STUDIES

4.1 Biocompatibility Testing

Biocompatibility testing fulfills the requirements of ISO 10993 and was performed in compliance with 21 CFR Part 58: Good Laboratory Practice Regulation. Testing was performed by North American Science Associates (NAMSA) per approved test protocols and reviewed by qualified personnel. Results of the ReSure Sealant biocompatibility testing demonstrate that ReSure Sealant is non-cytotoxic (ISO 10993-5), non-irritating (ISO 10993-10), non-sensitizing (ISO 10993-10) and elicits no acute systemic toxicity (ISO 10993-11). Based upon the series of biocompatibility tests performed and the history of safe use of component materials in other medical applications, the materials used to manufacture ReSure Sealant are acceptable for the intended use.

4.2 *In Vitro* Product Testing

In vitro bench studies of ReSure Sealant were conducted to evaluate the performance of both the ReSure hydrogel and Applicator. The purpose of these studies was to provide objective evidence that the product specification requirements identified in the ReSure Sealant Product Specification, namely the hydrogel performance specifications for mixing time, gel time, pot life, swelling, burst strength and diluent volume; and applicator performance specifications, namely applicator handle and foam tip integrity, application of gel with applicator and atraumatic tip testing were fulfilled. The test plan was developed based on assessment of key performance criteria as defined in the Product Specification, along with consideration of the device risk assessment (i.e., Failure Mode Effect Analysis). In addition to performance specification testing, further testing was performed to fully characterize the ReSure hydrogel properties such as pH, osmolality, and diffusion of low molecular weight molecules.

Based upon the results of the *in vitro* testing, consistent functional performance of the ReSure Sealant hydrogel and Applicator has been demonstrated which supports the use of ReSure Sealant when applied intraoperatively to clear corneal incisions with a wound leak demonstrated by Seidel test, and for prevention of postoperative fluid egress following cataract or intraocular lens placement surgery.

4.3 Animal Testing

Ocular Therapeutix conducted a series of preclinical studies to evaluate the *in vivo* performance and safety of ReSure Sealant. Specifically, these studies were designed to:

- Demonstrate the safety and performance of ReSure hydrogel when applied in a clinically relevant model;
- Evaluate the potential for extra- and intra-ocular toxicity caused by ReSure hydrogel;
- Demonstrate the sealing capabilities of ReSure hydrogel; and
- Demonstrate ReSure hydrogel is removable.

All animal testing was performed in compliance with 21 CFR Part 58: Good Laboratory Practice Regulation. Testing was performed per approved test protocols and reviewed by qualified personnel. Data from this series of animal studies provide objective evidence that ReSure Sealant is safe and effective for the intended use.

ReSure Sealant was tested for ocular toxicity and irritation in two worst-case scenarios: (1) maximum clinical dose applied to the surface of the cornea, and (2) with the liquid hydrogel injected into the anterior chamber. Slit lamp evaluations and histological review demonstrate even in these worst-case situations, ReSure hydrogel was well tolerated with no signs of ocular irritation or toxicity. Persistence of ReSure Sealant was evaluated in both rabbit and swine models. The device was present on the incision for the first few days after treatment generally corresponding to the period of epithelial healing. Further testing in a clinically relevant swine model demonstrated ReSure Sealant's ability to seal a full thickness clear corneal incision, as well as the ability to remove ReSure Sealant if required. A summary of the key animal studies is provided in **Table 2**.

Table 2: Summary of Animal Studies

Study Number	Study Summary
1	**Purpose:** Evaluate ocular irritation and persistence of the maximum clinical dose of ReSure Sealant **Study Design:** • 8 New Zealand White Rabbits each with one test eye and one control eye • Treatment: ReSure Sealant applied to a full thickness corneal incision, as well as to one additional topical location on the eye • Control: an untreated full thickness corneal incision in the contralateral eye • Follow-up evaluations: Days 1, 3, 7 and 14 o Evaluations for local reactivity, device persistence and healing via slit lamp exams o Day 14 all 8 rabbits terminated and incision sites processed for histopathology **Results:** • There were no findings indicative of potential ocular irritation. • ReSure Sealant was present over the incision in 3/8 eyes on Day 1 and was no longer present on the incision by Day 3 when all incisions received a maximum healing score (grade 3: 75-100% healed).
2	**Purpose:** Evaluate toxicity of an intraocular injection of ReSure Sealant **Study Design:** • 6 New Zealand White Rabbits each with one test eye and one control eye • Treatment: Single intraocular full dose injection (2.1µL) of a diluted solution of ReSure Sealant (prior to gelation) into the anterior chamber • Control: Single intraocular injection of 20µL Balanced Salt Solution in the contralateral eye • Follow-up evaluations: Hour 4 (IOP only), Days 1, 3, 7 and 14 o IOP measurements and slit lamp exams o Day 14 all 8 rabbits terminated and eyes processed for histopathology **Results:** • There were no adverse slit lamp findings and IOP measurements were equivalent between treatment groups, with no significant changes from pretreatment. • ReSure Sealant was well tolerated with no evidence of ocular irritation or toxicity following

Study Number	Study Summary
	an injection of ReSure Sealant in the anterior chamber.
3	**Purpose:** Evaluate incision sealing and persistence of ReSure Sealant **Study Design:** • 8 swine with one test eye and one control eye • Treatment: ReSure Sealant was applied to a full thickness corneal incision • Control: Suture was used to close a full thickness corneal incision in the contralateral eye • Wound leak assessment: Conducted immediately after application and again at Day 1via Seidel test while applying up to 1 ounce of force to the ocular surface • Follow-up evaluations: Daily on Days 1-7; slit lamp exams **Results:** • Leak rates were similar for the ReSure group (2/8) and suture group (3/8). • ReSure Sealant was present on all incisions at Day 1 and was no longer present by Day 2. • All eyes exhibited some re-epithelialization by Day 2 and received the maximum incision healing score (75-100% healed) by Day 3.

4.4 Sterilization, Packaging and Shelf-Life

ReSure Sealant is sterilized to a sterility assurance level (SAL) of 1×10^{-6} using a validated gamma irradiation process by a contract sterilization facility, STERIS-Isomedix Services.

ReSure Sealant is provided in a single use package with all necessary components. The device configuration consists of one plastic bottle/dropper filled with diluent solution, a plastic mixing tray with two wells containing lyophilized deposits of reactants (one blue deposit and one white deposit), and two Applicators. The two Applicators are secured together with an applicator holder. The mixing tray is packaged within a foil pouch that has an exterior pocket where the diluent bottle/dropper and Applicators are placed. The sealed foil pouch is then placed in a Tyvek/film pouch, providing a sterile barrier. ReSure Sealant will be shipped in boxed quantities of five pouched devices or ten pouched devices, together with one instructions for use. Pouched devices and each shelf box are individually labeled.

Initial commercialization is planned to be performed through a design controlled post-market surveillance plan/ limited market release. During this design control phase, ReSure Sealant will be labeled with 5 months shelf life. For the subsequently planned full market release, ReSure Sealant will be labeled with a minimum 9 months shelf life. Shelf-life testing includes hydrogel performance specifications for mixing time, gel time, pot life, swelling, burst strength and diluent volume; and Applicator performance specifications for applicator handle and foam tip integrity, application of gel with applicator and atraumatic tip testing; and package integrity testing. Package integrity testing included both seal strength testing and whole package integrity testing to ensure the ability of the Tyvek pouch to maintain device sterility throughout shelf-life, including worst case shipping and handling conditions. Additionally, peel strength testing was performed on the foil pouch to ensure the inert environment for the mixing tray is maintained across shelf life.

5.0 CLINICAL STUDY

The ReSure Sealant Pivotal Study was designed to evaluate safety and effectiveness of ReSure Sealant and to establish non-inferiority of the subject device to a control device (i.e., suture) for preventing incision leakage from clear corneal incisions within the first 7 days of surgery for patients undergoing uneventful clear corneal cataract surgery with phacoemulsification and IOL placement.

Data presented from the ReSure Sealant Pivotal Study are based upon the clinical study report included in this PMA P130004.

5.1 Study Design and Plan

This pivotal trial was a prospective, randomized parallel arm, controlled multicenter, subject-masked study in which 488 subjects who underwent cataract surgery were randomized and evaluated. The study was conducted at 24 investigational sites in the United States. Subjects meeting all preoperative and intraoperative eligibility criteria and determined to have a leaking incision via positive Seidel test were randomized in a 5:3 schema to receive ReSure Sealant or suture(s). A suture was selected as the comparator device for this study as it is generally considered the "gold standard" closure method for treatment of incisional leaks.

Incision leakage was assessed via a Seidel test intra-operatively and during follow-up visits. During the intra-operative evaluation, the Seidel test was administered in conjunction with an application of force near the incision using a standardized method. Post-operative evaluations were conducted at approximately 1 hour, 1, 3, 7, 14, 21 and 28 days post procedure and included keratometry, topography, BCVA, IOP and a slit lamp examination (SLE) with fluorescein staining. A standard Seidel test was repeated at 1, 3, 7 and 28 days post procedure to test for wound leakage. Acute incisional healing was assessed at Days 7 and 28. Additionally, subjects were required to complete an Ocular Comfort Index (OCI) OCI-Daily questionnaire once daily for postoperative Days 1-7 and the OCI-Weekly questionnaire at the Day 14, Day 21 and Day 28 visits as a patient reported outcome for assessment of ocular irritation/discomfort.

For subjects treated with ReSure Sealant with continued presence of the hydrogel material at the Day 28 visit, the subjects were to return at Days 45, 60 and 90 until the ReSure Sealant hydrogel was absent. Of note, no subject treated with ReSure Sealant in this study had hydrogel material present beyond the Day 28 visit and, therefore, reference to the Post-28 Day follow-up visits is appropriately excluded from this Executive Summary.

Subjects were not told which group they were assigned and steps were identified within the protocol to attempt to maintain subject masking throughout the duration of the study. A masking effectiveness assessment in which the subjects were asked to identify which treatment they believed they were assigned was performed at the Day 28 visit (or just prior to suture removal if premature removal was clinically indicated).

5.1.1 Subject Eligibility

Pre-Operative Inclusion Criteria

Subjects were eligible for inclusion in the study if they met all of the following criteria:

Pre-Operative Inclusion Criteria	
1	Subject must have been greater than or equal to 22 years of age.
2	Subject had a cataract and was expected to undergo clear corneal cataract surgery with phacoemulsification and implantation of a posterior chamber intraocular lens.
3	Subject was informed of the nature of the study and was able to comply with study requirements and provided written informed consent, approved by the appropriate Institutional Review Board (IRB).

Pre-Operative Exclusion Criteria

Subjects were to be excluded from the study if they met any of the following criteria:

Pre-Operative Exclusion Criteria	
1	Any intraocular inflammation in the study eye present during the screening slit lamp examination or presence of ocular pain in the operative eye as rated on the Ocular Comfort Index at the preoperative assessment.
2	Previous corneal or retinal surgery (laser or incisional) or planned multiple procedures (e.g., limbal relaxing incisions) during cataract surgery.
3	Previous ocular trauma if subject had visible scarring or any deformities due to the trauma.
4	Potential BCVA in fellow eye worse than 20/40 as assessed by the Investigator.
5	Presence of congenital or other ocular anomaly (e.g., keratoconus with evidence of corneal ectatic disease pterygium, recurrent erosions), corneal dystrophy (e.g., anterior basement membrane dystrophy, stromal or endothelial dystrophies). Pterygium were allowed provided they were not near the incision, did not contribute to the irregularities in the cornea, were a maximum of 2 mm on the cornea, and did not affect vision/in the visual axis.
6	Active or history of chronic or recurrent inflammatory eye disease (e.g., iritis, scleritis, uveitis, iridocyclitis, rubeosisiritis).
7	Evidence of acute external ocular infections, intraocular infection, dysthyroid ophthalmopathy, nasolacrimal duct obstruction, active chalazion, or uncontrolled blepharitis.
8	Uncontrolled and clinically significant dry eye syndrome.
9	Clinically significant guttae affecting corneal thickness (thickness < 475 or > 640 microns).
10	Glaucoma or subjects on any glaucoma medications.

Pre-Operative Exclusion Criteria	
11	Presence of ocular hypertension in the operative eye (IOP ≥ 25 mmHg).
12	Use of topical ocular steroids within 14 days and/or systemic steroids (excluding inhalants) within 30 days prior to surgery.
13	Use of prophylactic pain medications within one week prior to the Baseline/Screening Assessment through the 28 day follow-up period. This included prophylactic use of peri- and postoperative pain (analgesic) medications such as topical or systemic NSAIDS, opiates/nonopiates, and acetaminophen. Non-prophylactic pain medications (i.e., pain medication taken for pain that subject is experiencing) were allowed prior to and throughout the duration of the study. Medications taken for cardiac maintenance (e.g., 81 mg Aspirin) were allowed prior to and throughout the duration of the study.
14	Subject had insulin-dependent diabetes, proliferative diabetic retinopathy (PDR), compromised macular function or clinically significant macular edema (CSME).
15	Subject currently had suspected or known malignancy or was currently receiving antineoplastic therapy.
16	Subject had a compromised immune system or an autoimmune disease that in the opinion of the Investigator could affect the quality of the ocular surface.
17	Pregnant or breast-feeding women or women who wished to become pregnant during the length of study participation.
18	The Investigator determined that the subject should be not be included for reasons not already specified if the health of the subject or the validity of the study outcomes (e.g., ocular disease that would interfere with study evaluations, allergy to FD&C Blue #1) would be compromised by the subject's enrollment.
19	Subject had been previously enrolled in this clinical study, or was participating in another clinical trial during the follow-up period that could confound the treatment or outcomes of this investigation.

Intra-Operative Exclusion Criteria

All subjects who met any of the following intra-operative exclusion criteria were considered screen failures and were not eligible to be randomized in the study:

Intra-Operative Exclusion Criteria	
1	Incidental finding of preoperative exclusion criteria.
2	Subject determined not to be a suitable candidate for topical anesthesia.
3	Subject required multiple procedures (e.g., limbal relaxing incisions) during cataract surgery.
4	Subject had a floppy iris or required devices (iris hooks, etc.) or techniques not generally used in routine cataract surgery.
5	Subject had another intraoperative condition that in the opinion of the Investigator precluded further participation in the study (e.g., subjects with intraoperative complications such as posterior capsule rupture, anterior vitrectomy, torn or ruptured zonules, phacoemulsification burns, incisions larger than 3.5 mm or torn incisions should have been excluded).
6	Wound did not leak while applying force using the Calibrated Force Gauge.

5.1.2 Study Objective and Endpoints

The purpose of the ReSure Sealant Pivotal Study was to evaluate the safety and effectiveness of ReSure Sealant compared to suture(s) for preventing incision leakage from clear corneal incisions within the first 7 days of surgery for patients undergoing uneventful clear corneal cataract surgery with phacoemulsification and intraocular lens placement.

Primary Effectiveness Endpoint

The primary effectiveness endpoint was the proportion of eyes with any clear corneal incision/suture leakage as determined by a positive Seidel test indicating fluid egress within the first 7 days after surgery. Demonstration of non-inferiority was required to meet the primary endpoint objective and, if non-inferiority was demonstrated, superiority was to be tested.

Secondary Effectiveness Endpoints

- Surgically induced corneal astigmatism at Day 28
- Best corrected visual acuity worse than 20/40 at Day 1
- Best corrected visual acuity worse than 20/40 at Day 28

Tertiary Effectiveness Endpoints

- Presence of ReSure Sealant or suture(s) at every follow-up visit
- Presence of blue colorant in ReSure Sealant at every follow-up visit through Day 28

- Device ease of use: After each procedure, the surgeon was asked to rate the ease of use of ReSure Sealant or suture(s) as "very easy", "easy" or "difficult"

Safety Endpoints

- Corneal edema at Day 1 (moderate to severe stromal edema)
- Anterior chamber inflammation (defined as ≥ grade 2+ anterior chamber cells) at Day 1

5.1.3 Development of the Calibrated Force Gauge and Representative Force

In ophthalmic surgical practice, the integrity of clear corneal incisions is often tested with simple digital pressure, but this technique is variable and is likely to provide only a gross indication of wound integrity. Clinical studies have attempted to evaluate wound stability after cataract surgery with standard instruments including an irrigation cannula,[8] an ophthalmodynamometer (ODM)[24] and surgical sponge.[10,11,25] The major drawbacks associated with the use of these instruments is that they are not able to be sterilized and/or do not allow calibration or standardization of the amount of force applied.

A preferred technique is a wound challenge that is standardized, quantifiable, and reproducible. The Calibrated Force Gauge (CFG) was developed by Ocular Therapeutix specifically for standardizing wound leak testing in this clinical study (**Figure 5**). The CFG was reviewed with FDA for use in the ReSure Sealant Pivotal Study in order to ensure a standardized method for wound leak testing. The CFG is a modified, sterilizable orthodontic instrument that delivers controlled, measurable external force to the eye to standardize the method by which clear corneal cataract incisions are tested for integrity and leakage.[12] The CFG was also designed with a visual marking at 1 ounce to indicate that is the maximum force allowed for this study (**Figure 6**).

Figure 5: Calibrated Force Gauge

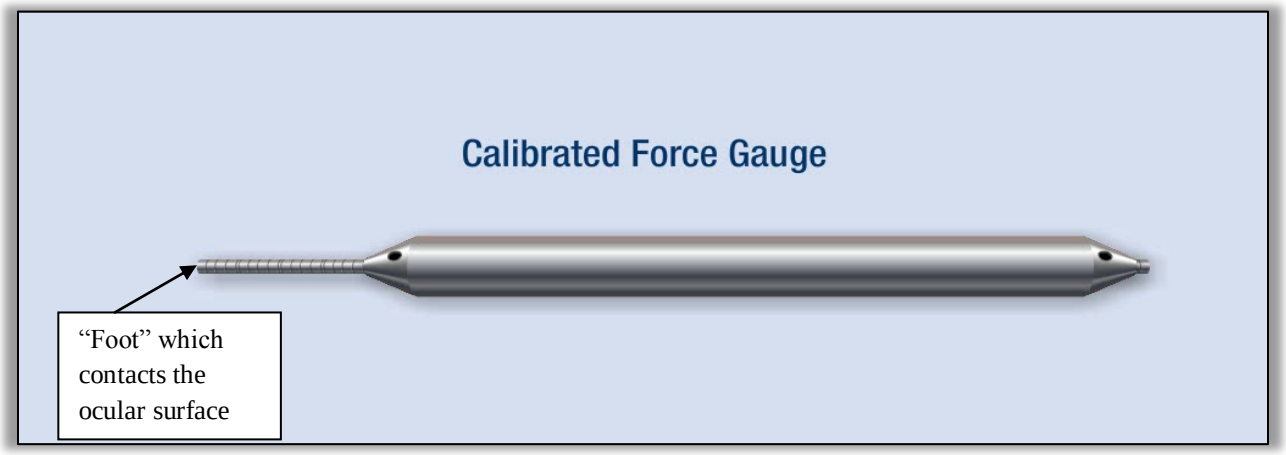
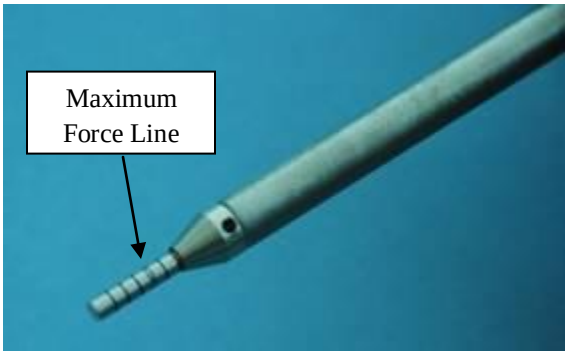


Figure 6: Calibrated Force Gauge Max Force Line Magnified



The methodology for performing a Wound Leak Assessment was standardized such that up to 1 ounce of force was applied for approximately 2-3 seconds at a distance of 0.5 mm away from the incision, with the Calibrated Force Gauge placed on the posterior aspects on the scleral side of the incision. Force was applied slowly and gently until a leak was observed or until the maximum force was achieved (i.e., 1 ounce of force or 4 lines with each line mark on the instrument calibrated to 0.25 ounces).

The location and duration of the leak test (posterior to the incision for approximately 2-3 seconds) was selected to mimic the evaluation performed with a Weck-Cel sponge. The globe was compressed with the CFG in the vicinity of the incision rather than elsewhere because this location represents the greatest likelihood for deformation of the incision and subsequent leakage. The force applied is physiologically relevant as the force the CFG generates results in an increase in IOP similar to which the operated eye may be exposed early after surgery via eye touching, rubbing and/or forceful blinking.[26,27] In a method development study the application of 1 ounce of force on the ocular surface using the CFG resulted in an average IOP of 43 mmHg[12], which is comparable to average IOP values reported during the direct application of light and firm digital forces on the eye (27 mmHg and 58 mmHg, respectively)[27] and squeeze blinking which can produce spikes of 50 mmHg to 110 mmHg.[28,29] The 1 ounce of force delivered by the CFG is significantly lower than the 4.4 ounces of force (4.5 kg/2.54 cm^2) that can be delivered to the surface of the eye during rotary knuckle rubbing.[26]

5.1.4 Wound Leak Assessment Methodology

Intra-operatively, the clear corneal incisions were first evaluated for the potential of leakage via a Seidel test using fluorescein staining with no provocation. If spontaneous leakage was noted from the incision, the leak was characterized as an "unprovoked" leak. If the wound did not leak without provocation, the wound was tested for leakage via a Seidel test using the Calibrated Force Gauge as previously described. Force was applied slowly until a leak was observed or until the maximum force (1 ounce or 4 lines) was achieved. In practice, a conservative strategy was used such that the number of lines of force needed to invoke a leak was rounded up to the next line (e.g., if leaking occurred with a light touch of the instrument representing less than 1 line of force, the amount of force necessary to invoke the leak was documented as "1 line", if the force was between line 1 and line 2, it was documented that "2 lines" of force were required).

For post-randomization assessments which were conducted after treatment was administered, the surgeon was instructed to take care not to place the Calibrated Force Gauge directly on ReSure Sealant hydrogel or the suture(s).

Post-operative wound leak assessments were performed only via Seidel test. The CFG was not used post-operatively.

5.1.5 Surgical Procedure

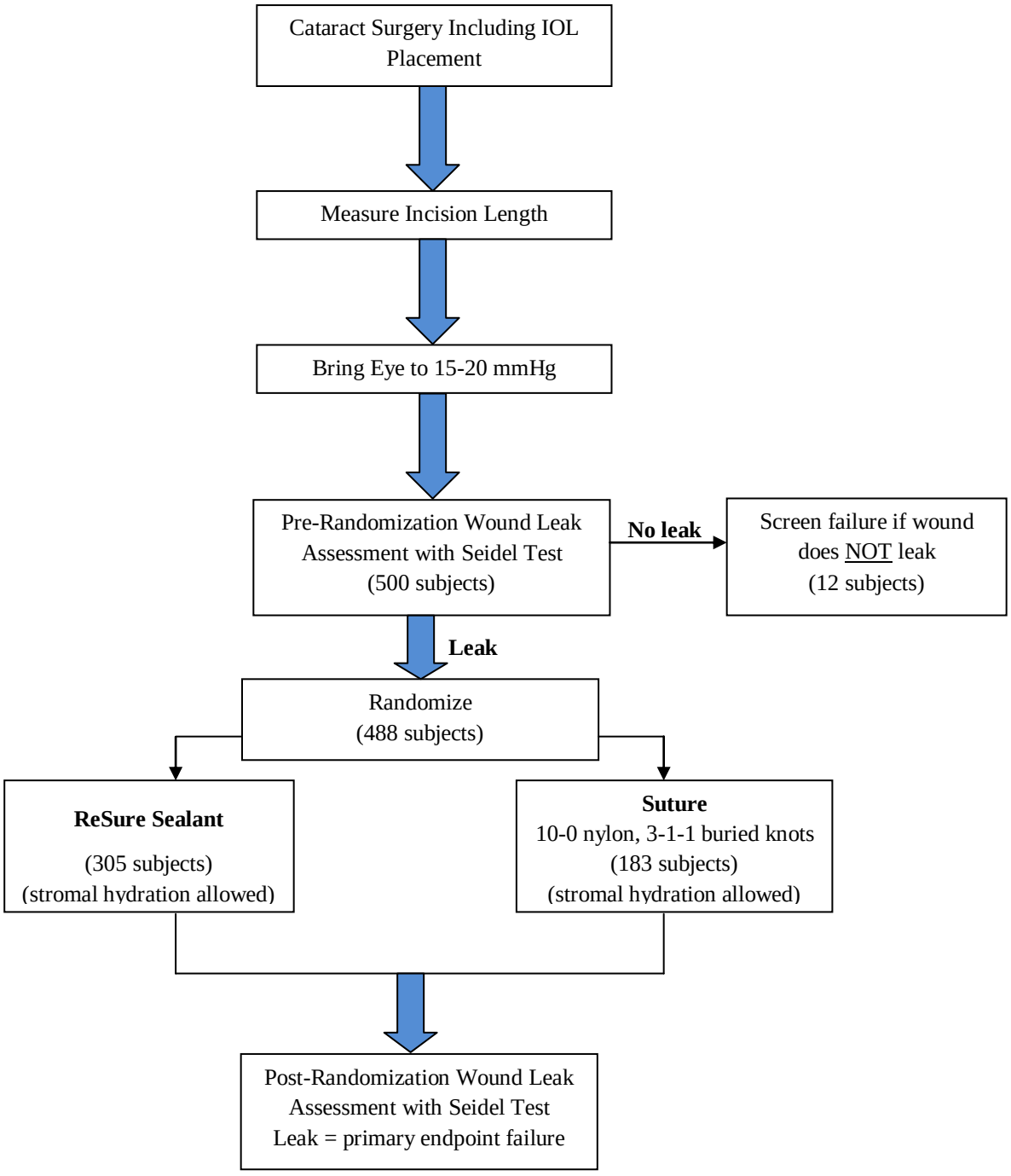
A flowchart of the surgical procedure and Wound Leak Assessment is provided in **Figure 7**. Cataract surgery was performed with topical anesthesia following standard operative techniques with the exception that no additional surgical procedures/incisions (e.g., limbal relaxing incisions) could be performed. Cataract extraction was performed through single plane incisions located in clear corneal tissue less than or equal to 3.5 mm in length as measured after IOL implantation using a calibrated measurement tool.

For the purpose of the ReSure Sealant Pivotal Study, a single plane incision was defined as an incision that extended into the corneal stroma then was angled down toward the anterior capsule of the lens (with no external groove). It was not defined as a straight "stab" incision.

At the conclusion of surgery, intraocular pressure was measured using a sterile tonometer (e.g., Ocular® Barraquer O.R. Tonometer – Craig Terry Model or equivalent) and the eye brought to physiologic pressure; i.e., 15 to 20 mmHg. A pre-randomization Wound Leak Assessment was then performed. Subjects meeting all preoperative and intraoperative eligibility criteria and determined to have a leaking incision via positive Seidel test (either unprovoked or following the standardized Wound Leak Assessment) were randomized to receive ReSure Sealant or suture(s). Subjects with a negative Seidel test indicating a sealed incision were excluded as a screen failure.

Following application of ReSure Sealant or suture(s), a post-randomization Wound Leak Assessment was performed to evaluate the integrity of the incision closure. Unless there was spontaneous fluid leakage (i.e., an unprovoked leak), pre and post-randomization Wound Leak Assessments were performed using the CFG. Any subject demonstrating a positive post-randomization Wound Leak Assessment and/or required additional treatment for a leaking incision following the post-randomization Wound Leak Assessment was considered a primary endpoint failure.

Figure 7: Flowchart of Surgical Procedure and Wound Leak Assessment



At the completion of surgery, a fourth generation fluoroquinolone antibiotic (e.g., gatifloxacin 0.3%, moxifloxacin 0.5%, etc.) and ophthalmic steroid drops (i.e., prednisolone acetate 1%) were to be administered into the operative eye. All subjects were required to use prednisolone acetate 1% ophthalmic steroid drops postoperatively on a tapered regimen as follows: four times a day through the Day 14 study visit, two times a day through the Day 21 study visit, and one time a day through the Day 28 study visit. Subjects were not permitted to use prophylactic pain medications until after they returned for the Day 28 study visit.

5.1.6 Study Treatments

ReSure Sealant was prepared and applied as follows. ReSure Sealant was mixed with the diluent in the mixing tray. To ensure a dry application site prior to application of ReSure Sealant, the Investigator was to ensure that the incision site was not actively leaking and was to remove any standing moisture from the surrounding conjunctival surface. Stromal hydration could be used as needed to ensure a dry surface. The liquid ReSure Sealant material was picked up onto the Applicator tip and applied over the length of the incision ensuring full coverage of the margins around the incision.

Subjects randomized to the Suture group were treated as follows. An atraumatic side cutting lancet needle with 10-0 nylon suture material (Angiotech Sharpoint™), provided by Ocular Therapeutix, was used. The suture was placed perpendicular to the incision and tied with 3-1-1 knots that were buried. Unless premature suture removal was clinically indicated, the suture(s) was to stay in place at least until the completion of the Day 28 follow-up visit, after which the suture(s) could be removed per the physician's standard of care. Stromal hydration could be used as needed.

To demonstrate effectiveness, the performance of ReSure Sealant was compared with the "gold-standard" for definitive CCI closure, i.e., sutured closure using a 10-0 nylon suture. The literature supports the use of 10-0 nylon sutures at the conclusion of corneal cataract surgery. [2,15,30] Although other types of sutures are used in some cataract surgeries, the 10-0 nylon suture is the standard suture type used to close corneal cataract surgery incisions when the incision requires a suture. The clinical protocol standardized and specified incision location, architecture, suture size and material, needle type, etc., so that data from multiple study sites could be pooled for statistical analyses.

5.1.7 Schedule of Study Assessments

The schedule of study visits and evaluations is shown in **Table 3** and **Figures 8 and 9**.

A subject was considered enrolled in the study at the time the subject signed the informed consent. Once a subject qualified for the study and was randomized, they were to be followed whether or not the subject received the study assigned treatment. Subjects who are enrolled but determined to be ineligible prior to randomization were considered eligibility failures and did not require study follow-up visits.

Table 3: Schedule of Assessments

Study Parameter	Baseline/ Screening Visit (within 30 days of surgery)	Procedure	1 Hr. Visit (45-90 min)	Day 1 Visit (20-28 hours)	Days 1 - 7	Day 3 Visit (3-5 days)	Day 7 Visit (6-8 days)	Day 14 Visit (13-15 days)	Day 21 Visit (20-22 days)	Day 28 Visit (25-30 days)
Informed Consent and HIPAA	X									
Eligibility Assessment	X	X								
Demographics	X									
Medical/Ophthalmic History (inc. cataract grade/etiology)	X									
Central Corneal Thickness (pachymetry)	X									
Keratometry	X			X		X	X			X
Topography	X			X		X	X			X
BCVA	X			X		X	X			X
IOP	X			X		X	X			X
Slit Lamp Examination (w/ fluorescein staining)	X			X		X	X	X	X	X
Dilated Fundus Exam	X									
Ocular Comfort Index	X[a]				X[b]			X[a]	X[a]	X[a]
Randomization		X								
Seidel Test for Pretreatment Wound Leak without/with CFG		X[c]								
Seidel Test for Post-treatment Wound Leak with CFG		X								
Seidel Test for Post-treatment Wound Leak without CFG				X		X	X			X
Presence of ReSure Sealant or suture(s)			X	X		X	X	X	X	X
Presence of Blue Color in ReSure Sealant			X	X		X	X	X	X	X
Wound Healing Assessment							X			X
Masking Effectiveness Assessment										X
Adverse Ocular Events		X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X		X	X	X	X	X

[a]Subjects completed the Ocular Comfort Index-Baseline and the Ocular Comfort Index-Weekly

[b]Subjects completed the Ocular Comfort Index-Daily

[c]Calibrated Force Gauge pretreatment was used only if the wound did not leak without the Calibrated Force Gauge

Figure 8: Study Flow Diagram – Through Randomization

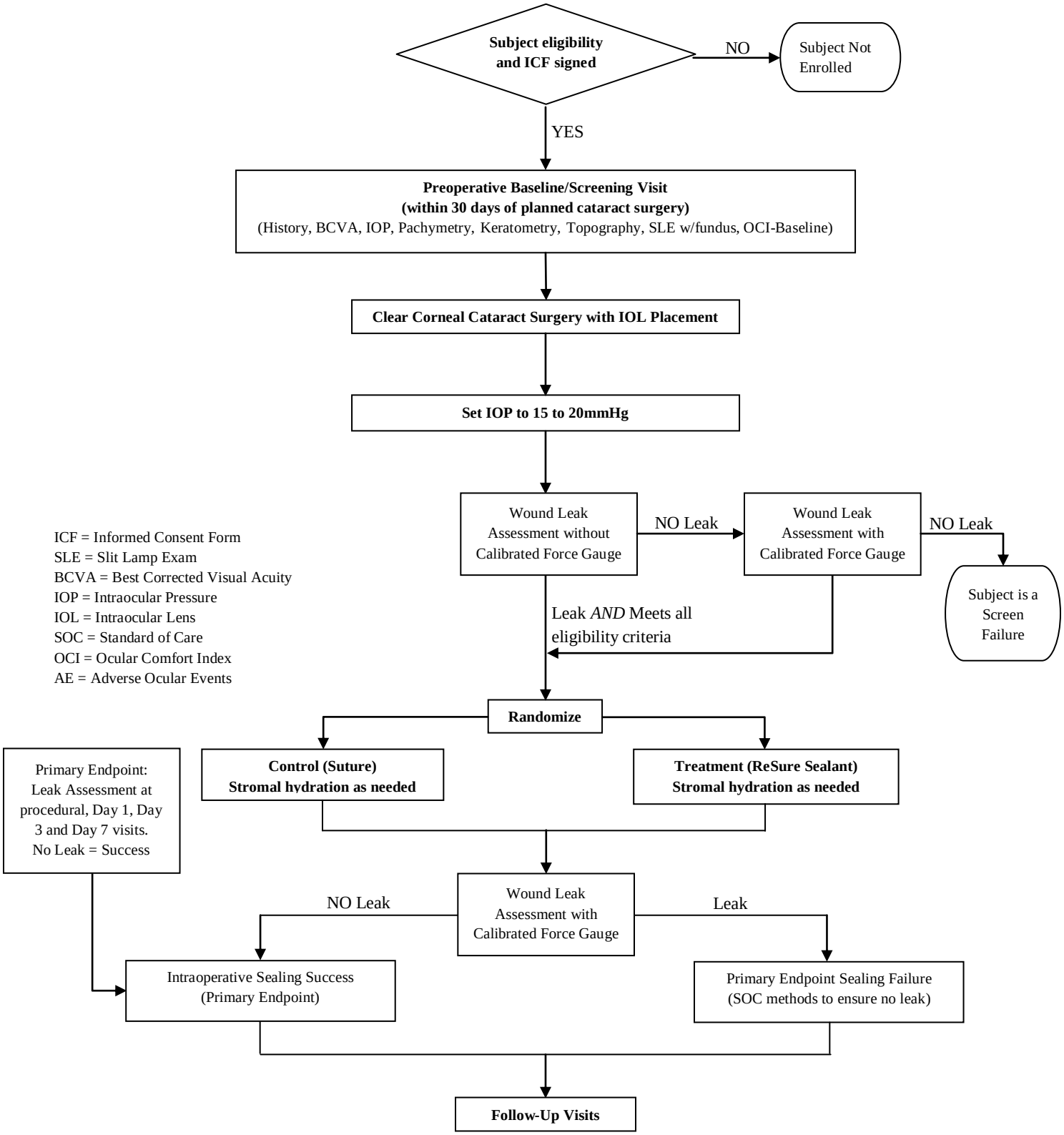
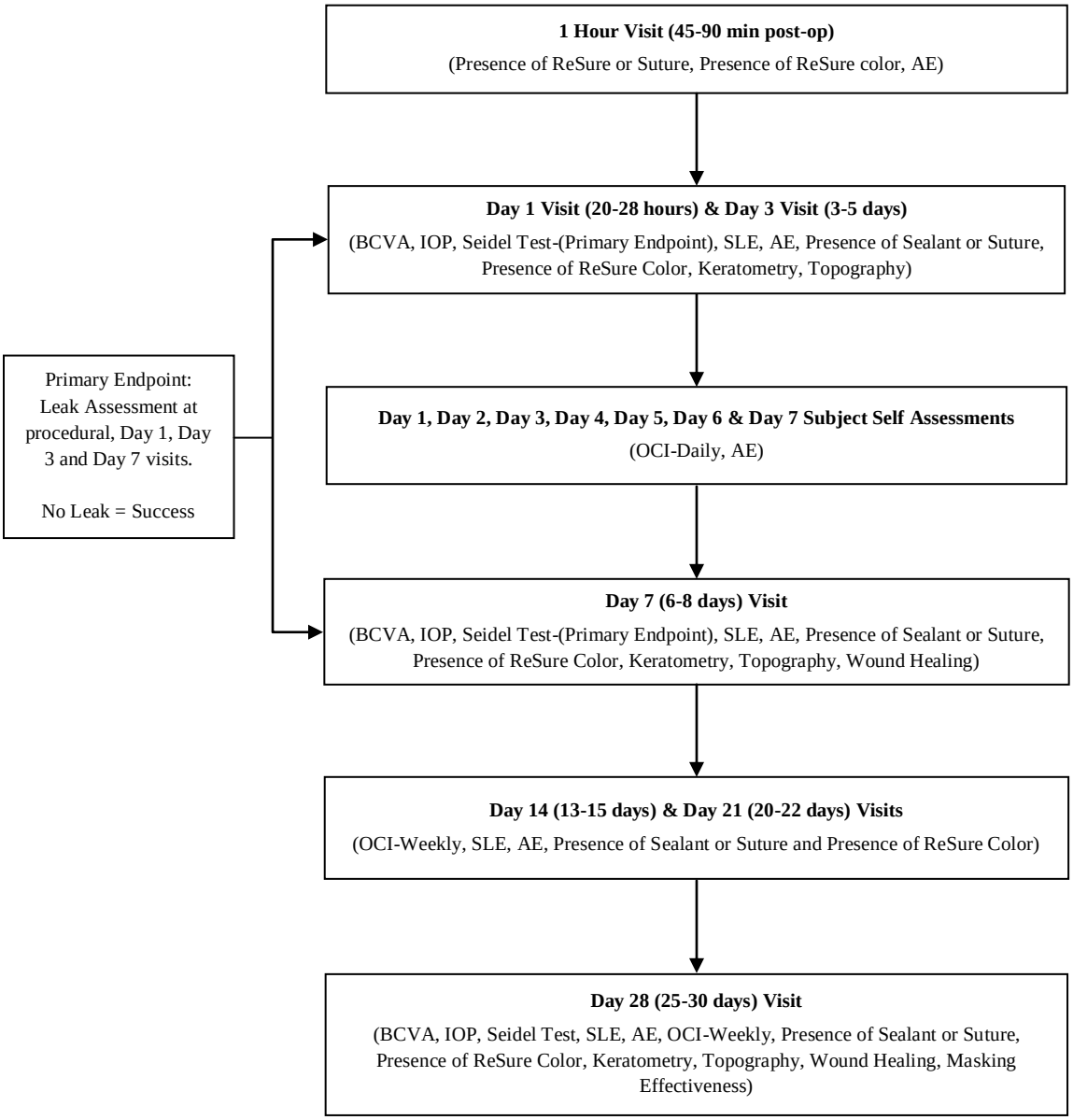


Figure 9: Study Flow Diagram – Follow-Up Visits



5.1.8 Statistical Methods

Statistical Analysis

The primary effectiveness endpoint was analyzed using a one-sided test for non-inferiority based on the normal approximation at the 0.05 significance level. The protocol specified that if non-inferiority was demonstrated, a two-sided test for superiority based on Fisher's Exact Test was to be performed at the 0.05 significance level. This endpoint is summarized by treatment group using counts and percentages, and an exact (Clopper-Pearson) two-sided 95% confidence interval (CI) for the true proportion is presented for each treatment group. Also, a 95% confidence interval based on the normal approximation is presented for the difference in the true proportions between treatments.

The secondary effectiveness endpoints were analyzed using the fixed sequence testing procedure. The secondary effectiveness endpoints were to be tested in the order listed in **Section 5.1.2** above. The surgically induced corneal astigmatism level at Day 28 was summarized by treatment group using descriptive statistics, and a 95% confidence interval for the mean was calculated based on the t-distribution for each treatment group. Also, a 95% confidence interval based on the normal approximation was presented for the difference in the true proportions between treatments. This endpoint was analyzed using an analysis of variance (ANOVA) model with terms for keratometer (IOL Master, LENSTAR LS900), treatment (ReSure Sealant, suture), and the keratometer by treatment interaction. A statistical significance level of 0.05 was used for testing the treatment effect. The proportion of eyes with BCVA worse than 20/40 at Day 1 and Day 28 were each analyzed using a two-sided test for superiority based on Fisher's Exact Test performed at the 0.05 significance level.

The safety endpoints were also analyzed using the fixed sequence testing procedure. The safety endpoints were to be tested in the order listed in **Section 5.1.2** above. The proportion of eyes with moderate to severe corneal edema at Day 1 was evaluated using a two-sided test for superiority based on Fisher's Exact Test performed at the 0.05 significance level. The proportion of eyes with anterior chamber inflammation at Day 1 was analyzed in the same manner.

The original study protocol included a brief plan for the statistical analysis and was approved by FDA in the IDE. Ocular Therapeutix subsequently produced a Statistical Analysis Plan (dated August 1, 2012) as a separate document to provide additional detail on the planned analyses presented originally in the study protocol. There were no changes or modifications to the Statistical Analysis Plan (SAP) at any time during the study. Any post hoc or unplanned analyses not identified in the Statistical Analysis Plan have been clearly identified as such in this Executive Summary.

Sample Size Determination

The sample size was determined based on considerations of both safety and effectiveness.

For safety, it was desired to be able to detect an adverse ocular event with true probability of occurrence among ReSure Sealant subjects of 1% with 95% probability. It was determined that this requires at least 299 ReSure Sealant subjects in the Safety Population. In order to ensure that at least 299 ReSure Sealant subjects were included in the Safety Population, it was decided to require that at least 303 subjects be randomized to receive ReSure Sealant.

Sample size calculations were then performed based on the following specifications:

- Parallel group design (one treated eye per subject)
- Primary effectiveness endpoint is leaking in eye (yes/no) within the first 7 days after surgery
- One-sided non-inferiority test based on normal approximation
- Non-inferiority margin of 0.05
- $\alpha = 0.05$ (one-sided)
- Power = 80%
- True proportion leaking in ReSure Sealant treated eyes = 0.20
- True proportion leaking in Control treated eyes = 0.25
- 5:3 (ReSure:suture(s)) allocation ratio to treatment groups
- Principal analysis of primary effectiveness endpoint based on the Per Protocol (PP) Population

The required total sample size based on the above specifications is 464 subjects in the PP Population. In order to provide for an expected 5% decrease between the number of randomized subjects and the number of subjects in the PP Population, this value was increased to 488 subjects. Thus, a total sample size of 488 randomized subjects (305 ReSure Sealant subjects and 183 suture(s) subjects) satisfies the requirements for both effectiveness and safety.

5.2 Study Subjects

5.2.1 Disposition of Subjects

A total of 583 subjects were consented (enrolled) for potential participation and 488 subjects were randomized (305 subjects to the ReSure group and 183 subjects to the Suture group). Of the six subjects that did not complete the study, four withdrew their consent. One subject discontinued from the study following the Day 3 visit due to development of a postoperative complication requiring follow-up by a retinal specialist (the complication was deemed unrelated to the study treatment). An additional subject was determined to be lost-to-follow-up after the Day 14 visit despite numerous attempts to contact the subject. Subject disposition is provided in **Table 4**.

Of note, only 487 unique study subjects participated in the study as 1 study participant of the 488 randomized was consented twice, was assigned two different subject numbers, and had both eyes randomized and treated with ReSure Sealant. The data for both eyes were included in the intent to treat (ITT) Population and Safety Population analyses, but only the data from the first enrolled eye were included in the PP Population analyses.

Table 4: Subject Disposition

Status	ReSure Sealant n (%)	Suture n (%)	Total n (%)
Consented Subjects			583
Randomized	305 (100.0)	183 (100.0)	488 (100.0)
Completed the Study	300 (98.4)	182 (99.5)	482 (98.8)
Discontinued from the Study	5 (1.6)	1 (0.5)	6 (1.2)

Note: Percentages are calculated based on the number of randomized subjects in each treatment group or overall, as appropriate.

There were high follow-up rates at every visit (> 98% for the total study cohort). Subject accountability is provided in **Table 5**.

Table 5: Cumulative Subject Accountability (ITT Population)

Parameter	ReSure Sealant (N=305)		Suture (N=183)		Total (N=488)	
Visit Compliance	***Eligible[a] (N)***	***Evaluated n (%)***	***Eligible[a] (N)***	***Evaluated n (%)***	***Eligible[a] (N)***	***Evaluated n (%)***
1 Hour Assessment	305	305 (100.0)	183	183 (100.0)	488	488 (100.0)
Day 1 Visit	305	305 (100.0)	183	183 (100.0)	488	488 (100.0)
Day 3 Visit	304	300 (98.7)	183	178 (97.3)	487	478 (98.2)
Day 7 Visit	304	302 (99.3)	183	179 (97.8)	487	481 (98.8)
Day 14 Visit	304	302 (99.3)	183	181 (98.9)	487	483 (99.2)
Day 21 Visit	303	298 (98.3)	182	180 (98.9)	485	478 (98.6)
Day 28 Visit	302	300 (99.3)	182	182 (100.0)	484	482 (99.6)

Note: The denominator for the calculation of percentages is the number of subjects eligible at the given visit.
[a]Subjects who withdrew consent were not deemed eligible for the visit.

5.2.2 Protocol Deviations

There were a total of 370 unique deviations among 244 subjects randomized. The 370 deviations represents an approximate 1% deviation rate, in consideration that overall there were greater than 33,184 opportunities for deviations based on the number of assessments/visits required throughout the study course for the 488 randomized subjects. **Table 6** summarizes the nature of protocol deviations reported by category.

Table 6: Protocol Deviations (ITT Population)

Deviation	ReSure Sealant (N=305) n (%)	Suture (N=183) n (%)	Total (N=488) n (%)
Total Subjects with Deviations			
Consent	4 (1.3)	3 (1.6)	7 (1.4)
Inclusion/Exclusion	15 (4.9)	11 (6.0)	26 (5.3)
Required Assessment Not Done[a]	51 (16.7)	30 (16.4)	81 (16.6)
Required Assessment Not Done within Specified Timeframe[b]	74 (23.9)	45 (24.6)	118 (24.2)
Procedure/ Device Related	4 (1.3)	3 (1.6)	7 (1.4)
Overall-Other[c]	47 (15.4)	27 (14.8)	74 (15.2)
Steroid Taper Regimen Deviation	33 (10.8)	22 (11.5)	55 (10.9)
Use of Prohibited Medications	7 (2.3)	4 (2.2)	11 (2.3)
Post-Operative Antibiotic Use (Not a 4th generation fluoroquinolone)	2 (0.7)	4 (2.2)	6 (1.2)
Out of Sequence Randomization[d]	4 (1.3)	2 (1.1)	6 (1.2)
Other Deviations	6 (2.0)	1 (0.6)	7 (1.4)

[a]Excludes 1 ReSure Sealant subject incorrectly categorized.

[b]Includes 2 ReSure Sealant subjects incorrectly categorized as "Required Assessment Not Done" and "Other".

[c]A subject can have more than one deviation in the "other" category.

[d]Includes 2 reports of randomization sequence break deviations reported in the category of "Procedure/Device Related".

Notes: (1) The percentages are based on the number of subjects in each treatment group or overall, as appropriate.
(2) A subject can have more than one type of protocol deviation, so the percentages may sum to more than 100%.
(3) Multiple deviations per subject within the same category are counted only once, including deviations from the randomization schema.

The majority of protocol deviations occurred early in the conduct of the study or during the early learning phase of each site's participation. Additional training of the study staff (i.e., re-review of the protocol and Good Clinical Practice (GCP) requirements) was implemented and preventative actions were taken when appropriate.

A total of 17 subjects (3.5% of the study population) listed below had a major protocol deviation as determined based on a blinded review of the data. Major protocol deviations were defined as a deviation that could confound analysis of the primary endpoint.

- 14 subjects with incomplete follow-up (i.e., missed Day 3 or Day 7 visits due to subject withdrawal or visit non-compliance).
- 1 subject who had been previously enrolled in the study for their fellow eye.
- 1 subject who did not receive assigned study treatment (ReSure Sealant) due to the fact that the ophthalmic surgeon was unable to achieve a dry ocular surface for application of the sealant.
- 1 subject with inadequate post-randomization Wound Leak Assessment as the Calibrated Force Gauge was only applied to line 3 (vs. to line 4) resulting in a less rigorous wound challenge.

Other protocol deviations included enrollment of ineligible subjects (e.g., prohibited medication usage, history of prior ophthalmic surgery), minor informed consent issues (e.g., incorrect version of informed consent form used, research staff inadvertently did not sign or date; note: all subjects gave consent), missed study visits, study visits not performed in the correct timeframe, incorrect application of ReSure Sealant, improper Wound Leak Assessment methodology, prohibited medication usage, and out of sequence randomization.

Of the 370 protocol deviations reported, only a small number were significant. None of the deviations compromised the safety of the study subjects or resulted in early discontinuation of the subjects from the study for safety reasons. Based on the nature and frequency of the deviations, there is no impact to the quality of the data, study results or conclusions that can be drawn from the study results.

Clinical Perspective: *Detailed and thorough review and analysis of protocol deviations demonstrate the integrity of the data and the scientific validity of the conclusions.*

5.2.3 Analysis Populations

Analyses are based on the following three study populations: Intent-to-Treat (ITT), Safety, and Per Protocol (PP). The numbers and percentages of subjects in each of these populations are summarized in **Table 7**.

Table 7: Analysis Populations

Parameter	Number of Subjects (%)			Comments
	ReSure Sealant n (%)	Suture n (%)	Total n (%)	
ITT Population	305 (100.0)	183 (100.0)	488 (100.0)	All randomized subjects: No subjects excluded.
Safety Population	304 (99.7)	183 (100.0)	487 (99.8)	All randomized and treated subjects: 1 ReSure Sealant subject excluded since the investigator was unable to achieve a dry ocular surface for application of ReSure Sealant and, therefore, the sealant was not applied to the eye.
PP Population	295 (96.7)	176 (96.2)	471 (96.5)	All randomized and treated subjects without a major protocol deviation based on a blinded review of the data: 17 subjects excluded based on deviations that could confound the analysis of the primary endpoint (see Protocol Deviations section above)

Note: Percentages are calculated based on the number of randomized subjects in each treatment group or overall, as appropriate.

5.2.4 Demographics

Demographic data are presented in **Table 8**. The subjects included in the two treatment groups were similar with respect to demographics as there were no statistical differences among the variables evaluated. Randomized subjects ranged from 31.9 years to 91.4 years of age; 83% were 60 years of age or older. Similar percentages of males and females were enrolled into each treatment group and the racial composition of both groups was very similar. Twenty percent (20%) of the patients were diabetic.

Table 8: Demographics (ITT Population)

Variable	ReSure Sealant (N=305)	Suture (N=183)	Total (N=488)	p-value[a]
Age (years)[b]				0.9610
Mean	68.80	68.84	68.81	
Median	69.08	69.08	69.08	
SD	8.93	8.55	8.78	
Min. – Max.	31.9-91.0	43.8-91.4	31.9-91.4	
Gender, n (%)				0.4516
Female	167 (54.8)	107 (58.5)	274 (56.1)	
Male	138 (45.2)	76 (41.5)	214 (43.9)	
Ethnicity, n (%)				0.2188
Hispanic or Latino	14 (4.6)	4 (2.2)	18 (3.7)	
Not Hispanic or Latino	291 (95.4)	179 (97.8)	470 (96.3)	
Race, n (%)				0.7001
White (Caucasian)	279 (91.5)	169 (92.3)	448 (91.8)	
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	
Asian	5 (1.6)	1 (0.5)	6 (1.2)	
Black or African American	12 (3.9)	9 (4.9)	21 (4.3)	
Other	9 (3.0)	4 (2.2)	13 (2.7)	
Tobacco Smoker, n (%)				0.4818
Current	41 (13.4)	18 (9.8)	59 (12.1)	
Past	114 (37.4)	73 (39.9)	187 (38.3)	
Never	150 (49.2)	92 (50.3)	242 (49.6)	
Diabetic, n (%)				0.7244
No	243 (79.7)	149 (81.4)	392 (80.3)	
Yes	62 (20.3)	34 (18.6)	96 (19.7)	
Insulin Dependent, n (%)				------
Yes	0 (0.0)	0 (0.0)	0 (0.0)	
No	62 (100.0)	34 (100.0)	96 (100.0)	
Uses Oral Hyperglycemic Agents, n (%)				0.6118
Yes	48 (77.4)	28 (82.4)	76 (79.2)	
No	14 (22.6)	6 (17.6)	20 (20.8)	

[a]p-value is from the two-sample t-test for continuous variables, testing for a difference in means between treatments, or from Fisher's Exact Test for categorical variables.

[b]Age = (Date of informed consent - date of birth)/365.25

5.2.5 Surgical Procedure Characteristics

Table 9 summarizes the surgical parameters compared. Surgical procedural characteristics were similar between the two treatment groups with respect to operative eye, incision length, incision location, and tunnel length. As mandated by the protocol, all subjects received single plane incisions in the clear cornea and the operative eyes were all brought to physiologic pressure (15 to 20 mmHg) prior to randomization.

Table 9: Summary of Procedural Characteristics (ITT Population)

Variable	ReSure Sealant (N=305)	Suture (N=183)	p-value[a]
Operative Eye, n (%)			0.3495
Right Eye (OD)	152 (49.8)	100 (54.6)	
Left Eye (OS)	153 (50.2)	83 (45.4)	
Incision in the Clear Cornea, n (%)			------
Yes	305 (100.0)	183 (100.0)	
No	0 (0.0)	0 (0.0)	
Incision Type, n (%)			------
Single Plane[b]	305 (100.0)	183 (100.0)	
Other	0 (0.0)	0 (0.0)	
Incision Location, n (%)			0.9059
Temporal	281 (92.1)	169 (92.3)	
Supra Temporal	14 (4.6)	10 (5.5)	
Nasally	1 (0.3)	1 (0.5)	
Supra Nasally	1 (0.3)	0 (0.0)	
Superior	8 (2.6)	3 (1.6)	
Estimated Tunnel Length (mm)			0.4914
Mean	2.25	2.28	
Median	2.50	2.50	
SD	0.48	0.49	
Minimum - Maximum	0.8-3.2	1.0-4.0	
Study Eye Brought to Physiological Pressure (15-20 mmHg), n (%)			------
Yes	305 (100.0)	183 (100.0)	
No	0 (0.0)	0 (0.0)	
Incision Length (mm)			0.2172
Mean	2.70	2.73	
Median	2.70	2.70	
SD	0.23	0.21	
Minimum - Maximum	1.9-3.5	2.0-3.5	

[a]p-value is from Fisher's Exact Test for categorical variables, testing for a difference between treatments in the proportions in each category, or from the two-sample t-test for continuous variables, testing for a difference in means between treatments.

[b]A single plane incision was defined as an incision that extended into the corneal stroma then was angled down toward the anterior capsule of the lens (with no external groove)

5.2.6 Pre-Randomization Wound Leak Assessment

Results from the pre-randomization intra-operative Wound Leak Assessment are presented in **Table 10**. The distribution of unprovoked and provoked leaks was similar between the two study groups with approximately equal proportions (i.e., 50% / 50%) of each type of leak within each treatment group. The majority of incisions leaked under ≤ 1 line of force equating to ≤ 0.25 ounces of force for 77% and 74% of the subjects assigned to the ReSure and Suture groups respectively. These data agree with a recent study reported by Mifflin *et al.* in which the authors evaluated the integrity of 2.8 mm uniplanar CCIs for patients having undergone routine cataract surgery. Incision leakage was evident in 85% of eyes confirmed to be sealed via conventional stromal hydration when firm downward pressure was applied with the tip of a cellulose sponge to the posterior lip of the incision (the maneuver the CFG challenge was designed to mimic but in a more controlled, standardized fashion).[11] The rate of intra-operative leaks is also similar to the rate of 67% reported in a recent study reported by Masket *et al.* in which the authors evaluated the integrity of clear corneal cataract incisions closed with stromal hydration using the same Wound Leak Assessment and CFG as in the ReSure Sealant Pivotal Study.[12]

Table 10: Pre-Randomization Wound Leak Assessments (ITT Population)

Parameter	Pre-Randomization		
	ReSure Sealant (N=305) n (%)	Suture (N=183) n (%)	p-value[a]
Wound Challenge			-----
No Leak[b]	0 (0.0)	0 (0.0)	
Leak	305 (100.0)	183 (100.0)	
Unprovoked - Seidel Test without Calibrated Force Gauge	151 (49.5)	93 (50.8)	
Provoked - Seidel Test with Calibrated Force Gauge	154 (50.5)	90 (49.2)	
Number of Lines of Force Applied with CFG			0.1528
1 line	85 (55.2)	42 (46.7)	
2 lines	42 (27.3)	21 (23.3)	
3 lines	21 (13.6)	22 (24.4)	
4 lines	6 (3.9)	5 (5.6)	
> 4 Lines	0 (0.0)	0 (0.0)	

[a]p-value is from Fisher's Exact Test, testing for a difference between treatments in the proportions in each category.
[b]Subject could not be randomized unless there was either an unprovoked or provoked leak.

Clinical Perspective: *Clear cataract incisions created in this study, which are generally believed to be self-sealing, were susceptible to leakage with minimal or no provocation. During the pre-randomization Wound Leak Assessment, half of the incisions leaked with no provocation, and the majority of incisions, approximately 75% of the entire study population, leaked when exposed to ≤ 0.25 ounces of force.*

5.2.7 Device Details

Details regarding device use are provided in **Table 11**. Application of ReSure Sealant had a very high rate of success with 303 of 305 subjects (99.3%) receiving successful coverage of the incision and margins around the incision. One subject did not receive treatment with ReSure Sealant as the Investigator was not able to achieve a dry surface for sealant application as required by the Instructions for Use. For another subject, application of ReSure Sealant was initiated but not completed as the ocular surface was not sufficiently dry.

Stromal hydration was used prior to the post-randomization Wound Leak Assessment in equal rates for the two treatment groups, with 74.4% of the ReSure group and 77.0% of the Suture group receiving stromal hydration. In the ReSure group, stromal hydration was primarily used to ensure a dry surface with no active leaks prior to device application as a dry surface is required per the Instructions for Use.

Table 11: Treatment Details (ITT Population)

Variable	ReSure Sealant (N=305) n (%)	Suture (N=183) n (%)
Received assigned study treatment		
Yes	304 (99.7)	183 (100.0)
No	1 (0.3)[a]	0 (0.0)
Dry ocular surface achieved prior to ReSure application		
Yes	303 (99.3)	------
No	2 (0.7)[b]	------
Number of ReSure Sealant or Suture Applications		
Mean	2.4	1.0
Median	2.0	1.0
SD	1.1	0.0
Min. – Max.	0 - 8	1 - 1
Stromal Hydration Used when Administering Treatment		
Yes	227 (74.4)	141 (77.0)
No	78 (25.6)	42 (23.0)

[a]ReSure Sealant could not be applied as the Investigator was not able to achieve a dry surface
[b]Application of ReSure Sealant was initiated, but not completed in one subject as the ocular surface was not sufficiently dry.

Upon request by FDA, a summary of the distribution of the number of ReSure Sealant applications and wound leak rate was generated and is provided in **Table 12**. It is important to note that "application" was defined in the ReSure Sealant Pivotal Study as taking ReSure hydrogel from the mixing tray well to the eye. An application does not indicate that the length of the incision had been covered. It may have taken more than one "application" or attempts at bringing the ReSure hydrogel from the mixing tray well to the eye in order to cover the full length of the incision including the margins around the incision as shown in **Figure 10**. Multiple applications do not denote multiple layers of ReSure hydrogel over the length of the incision. In fact, multiple layers do not improve the strength of ReSure Sealant. All applications of ReSure Sealant were administered intra-operatively within a period of a few seconds to minutes.

Figure 10: ReSure Sealant Coverage

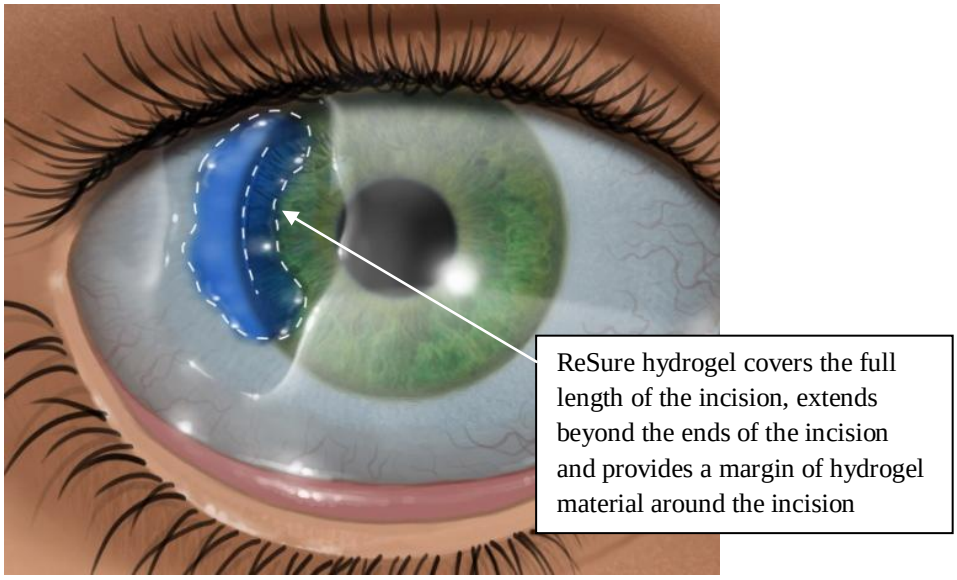


Table 12: Distribution of ReSure Sealant Applications and Leak Rates (ITT Population)

# Applications	n (%) N=304	n/N* (%)
1	54 (17.7)	1/52 (1.9)
2	128 (42.0)	3/125 (2.4)
3	76 (24.9)	5/76 (6.6)
4	32 (10.5)	2/30 (6.7)
5	11 (3.6)	1/11 (9.1)
6	0 (0.0)	0/0 (---)
7	2 (0.7)	0/2 (0.0)
8	1 (0.3)	0/1 (0.0)

*15 subjects had at least one missing value for leak evaluation from intra-operatively (post treatment) through Day 7. Because there is no imputation of missing values, such subjects are excluded from the analysis of the primary endpoint as missing.

There were several reasons for multiple applications including inadequate coverage of the full length of the incision and margins, having the hydrogel "gel" into a solid before a full application could be achieved in the short working time of the material (~15 seconds), and "run-off" of the ReSure hydrogel if the surface was not fully dry or if the fluid washed over the incision during application due to the position of the eye.

Over 95% of treatments with ReSure Sealant were completed with 4 applications or fewer with most (85%) of the subjects receiving 1-3 applications. Of the 14 subjects treated with greater than 4 applications, 8 of the 14 were within the surgeon's first 5 ReSure Sealant cases. In fact, 4 of these 8 subjects were the surgeon's first time using ReSure Sealant.

To further explore the potential impact of multiple applications on device effectiveness, the primary effectiveness endpoint of wound leak was analyzed for subjects treated with up to and including 2 applications compared to subjects treated with more than 2 applications. There are a small number of leaks overall and there were slightly more leaks in the group with greater than 2 applications. Multiple applications may be indicative of an incision that was not fully dry (i.e., weeping). ReSure Sealant may run off or not adhere as well to tissue that is wet. If initial applications were incomplete or had poor adhesion, applying additional hydrogel material may not rectify the situation as leakage may occur via the original interface where the sealant may not have been adherent to the tissue. Overall, the wound leak rates shown in **Table 13** confirm that ReSure Sealant effectiveness was not significantly impacted by the number of applications (*post hoc analysis,* p=0.0752).

Table 13: Primary Effectiveness Endpoint for Subjects Treated with ≤ 2 and > 2 Applications of ReSure Sealant (PP Population)

	≤ 2 applications n/N (%)	> 2 applications n/N (%)	p-value
Any clear corneal incision/suture leakage at any time within the first 7 days after surgery?	4/175 (2.3)	8/120 (6.7)	0.0752

Clinical Perspective: *ReSure Sealant had a high rate of successful administration (99.3%) and was effective in preventing wound leak for subjects with both low and high numbers of applications.*

5.2.8 Post-Randomization Wound Leak Assessment

Results from the post-randomization intraoperative Wound Leak Assessment are presented in **Table 14**. Within the Suture group, 25 of the 58 leaks (43%) occurred at ≤ 1 line of force (i.e., ≤ 0.25 ounces including the unprovoked leaks). Among the eyes demonstrating post-randomization leaks, there were a considerably higher percentage of sutured eyes leaking with 1, 2, and 3 lines of applied force compared to the ReSure group. These results demonstrate that not only do the sutured incisions have a higher incidence of wound leaks, but also less provocation is required for a leak to occur.

The rate of intra-operative leaks in the Suture group is similar to the rate of 24% reported in a recent study reported by Masket *et al.* in which the authors evaluated the integrity of clear corneal cataract incisions closed with suture using the same Wound Leak Assessment and CFG as in the ReSure Sealant Pivotal Study.[12] The wound leak rates for both the ReSure group and the Suture group were significantly less than the 67% leak rate for clear corneal cataract incisions closed with stromal hydration alone. [12]

It was left to individual surgeon discretion whether additional incisional closure measures were used if a leak was observed during the post-randomization Wound Leak Assessment. Of the 11 ReSure Sealant subjects with positive post-randomization Wound Leak Assessments, 3 were treated with additional stromal hydration and 2 incisions were sutured closed. Within the Suture group, of the 58 leaks, stromal hydration was used to treat 21 (36.2%) of the leaking incisions and additional sutures were used to treat 2 (3.4%).

Table 14: Post-Randomization Wound Leak Assessments (ITT Population)

Parameter	Post-Randomization		
	ReSure Sealant (N=305) n (%)	Suture (N=183) n (%)	p-value[a]
Wound Challenge			<0.0001
No Leak	293 (96.4)	125 (68.3)	
Leak	11 (3.6)	58 (31.7)	
Unprovoked - Seidel Test without Calibrated Force Gauge	1 (0.3)	4 (2.2)	
Provoked - Seidel Test with Calibrated Force Gauge	10 (3.3)	54 (29.5)	
Number of Lines of Force Applied with CFG[b]			<0.0001
1 line	3 (1.0)	21 (11.7)	
2 lines	3 (1.0)	11 (6.1)	
3 lines	3 (1.0)	15 (8.4)	
4 lines	294 (97.0)	131 (73.2)	
> 4 Lines	0 (0.0)	1 (0.6)	

[a]p-value is from Fisher's Exact Test, testing for a difference between treatments in the proportions in each category.
[b]Number of lines of force applied not available for 1 subject who could not have ReSure Sealant applied as the Investigator was not able to achieve a dry surface for sealant application

Clinical Perspective: *Sutured incisions have a higher incidence of wound leaks and significantly less provocation is required for a leak to occur in the Suture group.*

5.3 Effectiveness Results

5.3.1 Analysis Population

The Intent-to-Treat Population is defined to be all randomized subjects. The ITT Population is represented by 305 ReSure Sealant subjects and 183 Suture subjects for a total of 488 subjects. All effectiveness endpoints were analyzed based on the ITT Population, and subjects were analyzed according to their randomized treatment assignment. For the primary effectiveness endpoint, the analysis based on the PP Population is considered the primary analysis (since it is more conservative than the ITT analysis when assessing non-inferiority). For all other effectiveness endpoints, the analyses based on the ITT Population are considered the primary analyses.

The Per Protocol Population is defined to be all subjects in the ITT Population with no major protocol deviations. The PP Population is represented by 295 ReSure Sealant subjects and 176 Suture subjects for a total of 471 subjects. All effectiveness endpoints were also analyzed based on the PP Population, and

subjects were analyzed according to their randomized treatment assignment. For the primary effectiveness endpoint, the analysis based on the PP Population is considered the primary analysis. The reason for considering the analysis based on the PP Population as the primary analysis is that the principal test for the primary endpoint is a test of non-inferiority, and, for tests of non-inferiority, it is generally thought to be more conservative to use the PP Population rather than the ITT Population. For all other effectiveness endpoints, the analyses based on the PP Population are considered secondary analyses.

5.3.2 Primary Effectiveness Endpoint

As summarized in **Table 15**, the event rate for clear corneal incision leakage in the PP Population as determined by a positive Seidel test indicating fluid egress at any time within the first 7 days after surgery was 4.1% for subjects treated with ReSure Sealant compared to 34.1% for subjects who had their incisions sutured. ReSure Sealant was determined to be non-inferior ($p<0.0001$) and superior ($p<0.0001$) to sutures for prevention of clear corneal incision leakage. Similar results for both the tests of non-inferiority ($p<0.0001$) and superiority ($p<0.0001$) were observed for the ITT Population providing robust evidence for the effectiveness of ReSure Sealant.

The majority of wound leaks observed in both treatment groups were noted intra-operatively following the post-randomization Wound Leak Assessment (91.7% and 96.7% for the ReSure and Suture groups respectively). There was 1 later leak detected via a positive Siedel test at Day 3 within the ReSure group. The sealant was noted to be absent at the Day 3 visit and IOP was within normal physiologic limits (16 mmHg). At an unscheduled visit performed 2 days following the Day 3 visit, the subject continued to be Seidel positive, so the incision was sutured. No leak was detected at the Day 7 visit. Within the Suture group, two subjects had later leaks at Day 7. IOP was within normal physiologic limits for both subjects (12 mmHg and 17 mmHg). No further action was taken. Both subjects were Seidel negative at the Day 28 visit. A post hoc analysis was performed on the subset of post-operative leaks only and ReSure Sealant was demonstrated to be non-inferior to suture for the subset of post-operative leaks (0.3% vs. 1.1%, respectively; $p<0.0001$).

Of note, although approximately 75% of subjects treated with suture also received stromal hydration, despite taking these measures approximately one third of subjects (34.1%) experienced a wound leak.

Table 15: Primary Effectiveness Endpoint (PP Population)

Variable	ReSure Sealant (N=295)	Suture (N=176)	Difference in % (Suture - ReSure Sealant) and 95% CI[a]
Any clear corneal incision leakage at any time within the first 7 days after surgery, n/N (%)	12/295 (4.1)	60/176 (34.1)	30.0 (22.7, 37.4)
95% CI for %[b]	(2.1 , 7.0)	(27.1 , 41.6)	
p-value[c]			<0.0001
p-value[d]			<0.0001
Day Leakage First Occurred, n (%)			
Day 0	11 (91.7)	58 (96.7)	
Day 1	0 (0.0)	0 (0.0)	
Day 2	0 (0.0)	0 (0.0)	
Day 3	1 (8.3)	0 (0.0)	
Day 4	0 (0.0)	0 (0.0)	
Day 5	0 (0.0)	0 (0.0)	
Day 6	0 (0.0)	0 (0.0)	
Day 7	0 (0.0)	2 (3.3)	

[a]Confidence interval based on the normal approximation.
[b]Clopper-Pearson exact confidence interval for a binomial proportion.
[c]p-value from a one-sided normal approximation test of non-inferiority of ReSure Sealant to suture with respect to a binomial proportion, with a non-inferiority margin of 0.05.
[d]p-value from a two-sided test for superiority based on Fisher's Exact Test, testing for a difference in proportions between treatments.

An analysis was performed to evaluate the interaction between treatment and investigative site. No statistically significant interaction was detected (p=0.2985) demonstrating that there were no significant differences among sites with respect to the treatment effect.

In response to a request by FDA, the primary endpoint outcomes were stratified by gender, age, site, and site enrollment. There were consistently lower leak rates in the ReSure group when evaluated by gender, age and site enrollment subgroups of low and high enrolling centers. The results are summarized in **Table 16.**

Table 16: Summary of Primary Effectiveness Endpoint Outcomes Stratified by Site, Site Enrollment, Age and Gender

Stratification	Findings From Full Study Cohort Confirmed?	Comments
By Gender	Yes	• ReSure Sealant is demonstrated to be non-inferior to suture control for both male and female patients ($p < 0.0001$) • Leak rates were substantially lower in the ReSure group compared to the Suture group for both genders (**Table 17)**
By Age	Yes	• ReSure Sealant is demonstrated to be non-inferior to suture control for patients <60 years ($p= 0.0050$), 60-69 years ($p<0.0001$), and 70-79 years ($p<0.0001$) • Octogenarians (≥ 80 years) had fewer wound leaks in the ReSure group, but the sample size within this strata (n=40) is too small to demonstrate a statistically significant reduction in post-operative wound leak rates.
By Site	Yes	• 21 of 24 sites have ReSure leak rates ≤ suture leak rates • 2 sites enrolled only one subject so a comparison between groups cannot be made • 1 site had leak ReSure leak rate (1/13 or 7.7%) ≥ suture (0/8 or 0%)*
By Small and Large Sites	Yes	• ReSure Sealant is demonstrated to be non-inferior to suture for both low (≤10 subjects) and high (>10 subjects) enrolling sites ($p = 0.0006$ and $p < 0.0001$, respectively)

* The patient population and surgical details of the subjects treated at this site were reviewed and there do not appear to be any characteristics that are different from the other sites.

Table 17: Primary Endpoint Stratified by Gender

Female		Male		p-value
ReSure Sealant	**Suture**	**ReSure Sealant**	**Suture**	
6/163 (3.7)	34/101 (33.7)	6/132 (4.5)	26/75 (34.7)	<0.0001[1] <0.0001[2]

(1) p-value from a one-sided normal approximation test of non-inferiority of ReSure Sealant to suture with respect to a binomial proportion, with a non-inferiority margin of 0.05.
(2) p-value from a two-sided test for superiority based on Fisher's Exact Test, testing for a difference in proportions between treatments.

Clinical Perspective: *ReSure Sealant was demonstrated to be more effective than sutures for the prevention of clear corneal incision leakage in both the PP and ITT Populations.*

5.3.3 Secondary Effectiveness Endpoint

Three secondary effectiveness endpoints were pre-specified in the protocol, including:

- Surgically induced corneal astigmatism at Day 28
- BCVA worse than 20/40 at Day 1

- BCVA worse than 20/40 at Day 28

There were no statistical differences between treatment groups for any of the secondary effectiveness endpoint parameters evaluated (**Table 18**). These secondary effectiveness endpoints were pre-specified in the protocol for potential inclusion in the labeling on the chance that the results favored the ReSure Sealant. However, the study was not powered for these endpoints or inherently designed to investigate these secondary parameters as doing so would have required additional rigorous controls over the variables that may impact these analyses adding complexity to the study while adding no value to assessment of the primary endpoint.

Table 18: Secondary Effectiveness Endpoints (ITT Population)

Variable	Statistic	ReSure Sealant (N=305)	Suture (N=183)	Difference in Means or % (Suture - ReSure Sealant) and 95% CI[a]
1. Surgically induced corneal astigmatism at Day 28	N	288	177	
	Mean	0.600	0.597	-0.003 (-0.087, 0.082)
	Median	0.504	0.489	
	SD	0.454	0.442	
	Min- Max	0.06-3.25	0.02-2.66	
	95% CI for Mean[b]	(0.547, 0.652)	(0.531, 0.662)	
	p-value[c]			0.7997
	p-value[d]			0.1500
	p-value[e]			0.7732
2. BCVA worse than 20/40 at Day 1	n/N (%)	48/304 (15.8)	30/183 (16.4)	0.6 (-6.1, 7.4)
	95% CI for %[f]	(11.9 , 20.4)	(11.3 , 22.6)	
3. BCVA worse than 20/40 at Day 28	n/N (%)	10/300 (3.3)	7/180 (3.9)	0.6 (-2.9, 4.0)
	95% CI for %[f]	(1.6 , 6.0)	(1.6 , 7.8)	

[a]Confidence interval based on the normal approximation for categorical variables and on the t-distribution for continuous variables.
[b]Confidence interval based on the t-distribution.
[c]p-value for effect of treatment from ANOVA model with terms for treatment, keratometer (IOL Master, LENSTAR LS 900) and the treatment by keratometer interaction.
[d]p-value for effect of the keratometer from ANOVA model with terms for treatment, keratometer (IOL Master, LENSTAR LS 900) and the treatment by keratometer interaction.
[e]p-value for interaction term from ANOVA model with terms for treatment, keratometer (IOL Master, LENSTAR LS 900) and the treatment by keratometer interaction.
[f]Clopper-Pearson exact confidence interval for a binomial proportion.

In response to a request by FDA, the secondary effectiveness endpoint outcomes were stratified by site. The results stratified by study site support the findings of non-significance reported for the full study cohort. Although there are a few isolated occurrences of secondary effectiveness endpoints at particular sites being significant, the large majority indicate that there are no significant differences between the ReSure Sealant group and the Suture group for any of the secondary effectiveness endpoints.

In response to an additional request by FDA, two sensitivity analyses were performed on the surgically induced astigmatism (SIA) endpoint. In the first analysis, subjects who completed the Day 28 Visit who had missing SIA data at Day 28 were assigned a value of 0 for this endpoint, indicating that there is no astigmatism, and in the second analysis they were assigned a value of 1.55 (selected because only 5% of the data in the study were worse (i.e., greater) than 1.55). The results of the both sensitivity analyses were similar to the results of the original analysis. It can be concluded that the missing data did not impact the original analysis, thereby confirming there is no difference in SIA at Day 28 between the treatment groups.

5.3.4 Tertiary Effectiveness Analyses

Presence of ReSure Sealant (and Blue Visualization Aid)/Sutures at Follow-Up Visits

Data for device presence is shown in **Table 19**. The blue visualization aid was present in 6.5% of subjects on the Day 1 visit and was not observed in any subjects on the Day 3 visit.

Table 19: ReSure Sealant Presence Data (ITT Population)

Visit	ReSure (N=305) n (%)	Suture (N=183) n (%)
1 Hr	302 (99.0)*	183 (100.0)
Day 1	232 (76.1)	183 (100.0)
Day 3	94 (31.3)	173 (97.2)
Day 7	8 (2.6)	174 (96.1)
Day 14	0 (0.0)	172 (94.5)
Day 21	0 (0.0)	164 (90.6)
Day 28	0 (0.0)	159 (87.4)

*****The 3 eyes without ReSure Sealant at this time point include one subject who did not receive treatment, one subject who received only partial treatment as ReSure administration was stopped prematurely due to lack of a dry surface, and one subject who had ReSure removed intra-operatively after the Wound Leak Assessment demonstrated a leak.

Clinical Perspective: *The observed persistence of ReSure Sealant is clinically relevant in that it covers the clear corneal cataract incision for the first few post-operative days while the epithelium is healing, which is the period that incisions are most vulnerable to leakage.*

The protocol dictated that unless removal was clinically indicated, sutures were to remain in place for the duration of the study. However by the Day 28 visit, 23 of the 183 (12.6%) subjects treated with sutures had the sutures prematurely removed. Reasons cited for premature suture removal include: infection, complaints of foreign body sensation (FBS), discomfort or irritation/suture sensation and/or conjuctival injection or mucus development around the suture, suture-related issues (suture elevated, loose or broke) and in 1 case corneal astigmatism.

Partial removal of ReSure Sealant was performed for 1 subject. On the second post-operative day the subject presented with a foreign body characterized as 95% of the study article that had disconnected from the site of placement, with 5% remaining on the site of placement. The disconnected material was removed with forceps. Upon removal, the foreign body event was resolved without any residual effects.

Device Ease of Use

Across the 24 investigative sites, 41 Investigators administered the study treatment and provided feedback on ease of use. The results are summarized in **Table 20**.

Table 20: Summary of Device Ease of Use (ITT Population)

Device Ease of Use	ReSure Sealant (N=305) n (%)	Suture (N=183) n (%)
Very Easy	166 (54.8)	75 (41.0)
Easy	119 (39.3)	98 (53.6)
Difficult	18 (5.9)	10 (5.5)

Clinical Perspective: *ReSure Sealant is at least as easy to apply compared with suture application, despite the fact that the clinical experience includes the first use/learning curve with ReSure Sealant.*

5.3.5 Effectiveness Conclusions

The following conclusions can be stated from the effectiveness analysis:

1. The event rate for clear corneal incision leakage as determined by a positive Seidel test indicating fluid egress at any time within the first 7 days after surgery was 4.1% for subjects treated with ReSure Sealant compared to 34.1% for subjects who had their incisions sutured. Therefore, it can be concluded that ReSure Sealant **is not inferior** to sutures for prevention of clear corneal incision leakage ($p<0.0001$). The performance of ReSure Sealant relative to the suture control has been established, the primary objective of the study has been satisfied, and the study is considered a success with respect to the primary effectiveness endpoint.

2. Having passed the test for non-inferiority for the primary effectiveness endpoint, an *a priori* analysis of superiority was performed. The incidence of clear corneal leakage within the first 7 days after surgery was determined to be statistically significantly less for subjects treated with ReSure Sealant ($p<0.0001$), demonstrating that ReSure Sealant **is more effective** than sutures for mitigating clear corneal incision leakage.

3. Clear cataract incisions created in this study, which are generally believed to be self-sealing, were susceptible to leakage with minimal or no provocation. During the pre-randomization Wound Leak Assessment, half of the incisions leaked with no provocation, and the majority of incisions, 77% and 74% respectively for the ReSure and Suture groups, and approximately 75% of the entire study population, leaked when exposed to minimal force (i.e., ≤ 1 line equating to ≤ 0.25 ounces of force).

4. Results from the post-randomization intraoperative Wound Leak Assessment demonstrated that within the Suture group, 25 of the 58 leaks (43%) leaked at ≤ 1 line of force (i.e., ≤ 0.25 ounces including the unprovoked leaks). Among the eyes demonstrating post-randomization leaks, there was a higher relative percentage of sutures leaking with less force; i.e., 1, 2, and 3 lines of applied force compared to the ReSure group. These results demonstrate that not only do the sutured incisions have a higher incidence of wound leaks, but also significantly less provocation is required for a leak to occur in the Suture group.

5. The proportion of responses for "Very Easy" to use is slightly higher for ReSure Sealant (54.8% vs. 41.0%). Overall it can be concluded that ReSure Sealant is at least as easy to apply compared with suture application, despite the fact that the clinical experience includes the first use/learning curve with ReSure Sealant.

6. The presence of ReSure Sealant can be characterized as 1 to 3 days, which corresponds with the period of epithelial healing. The hydrogel sealant was not observed to be present in visits beyond the Day 7 visit. The observed persistence of ReSure Sealant is clinically relevant in that it covers the clear corneal cataract incision while the epithelium is healing, which is the period that incisions are most vulnerable to leakage. ReSure Sealant was partially removed manually from 1 eye due to foreign body sensation demonstrating that, if necessary, the product can be removed.

7. This was a multicenter clinical study involving participation from 24 investigative sites. There were no significant differences among sites, site size, age and gender with respect to treatment effect demonstrating that ReSure Sealant effectiveness was not influenced by these parameters.

8. Effectiveness analyses outcomes were consistent for both the PP Population and ITT Population, providing robust evidence for the effectiveness of ReSure Sealant.

5.4 Safety Results

5.4.1 Analysis Population

The Safety Population is defined as all treated subjects. The Safety Population is represented by 304 ReSure Sealant subjects and 183 Suture subjects for a total of 487 subjects. One ReSure subject was excluded from the Safety Population. After being randomized to receive ReSure Sealant, the subject was not treated with the study device as a dry ocular surface could not be achieved as required by the protocol. All of the safety analyses were conducted based on the Safety Population, and subjects were analyzed according to the actual treatment received (ReSure Sealant or suture(s)).

5.4.2 Safety Endpoints (Pre-specified)

There were no statistically significant differences between the two groups for the endpoints that had been established *a priori* for potential inclusion in the product labeling: 1) incidence of corneal edema (moderate to severe stromal edema) at Day 1 or 2) ≥ grade 2+ anterior chamber inflammation at Day 1.

5.4.3 Additional Safety Outcomes

Subjects underwent several safety assessments inclusive of thorough ophthalmic examinations including a slit lamp examination, BCVA, manifest refraction, keratometry, topography, tonometry, assessment of ocular symptoms via the OCI, wound leak and wound healing as well as review of spontaneously reported adverse ocular events. Results from these evaluations were similar between treatment groups. The findings indicate that ReSure Sealant is well tolerated and does not raise any safety concerns.

5.4.4 Summary of Adverse Ocular Events

As summarized in **Table 21**, the overall incidence of adverse ocular events reported for subjects treated with ReSure Sealant was significantly lower than for subjects treated with suture (22.7% vs. 45.4%, $p<0.0001$). This difference in adverse ocular event rate between the two groups is attributed primarily to the higher incidence of device-related adverse events in the Suture group. Within the ReSure group the percentage of subjects experiencing device-related AEs was significantly lower than for the Suture group (1.6% vs. 30.6%, $p<0.0001$). Excluding the adverse ocular events for subjects in the Suture group that were device related or with "unable to determine" relationship (i.e., the events of subconjunctival hemorrhage, eye irritation, eye pain and others), there is no difference in between the ReSure group (22.7%) and Suture group (21.9%) for the remaining events (*post hoc* analysis; Fisher's Exact Test; $p=0.9107$).

Table 21: Overall Summary of Adverse Ocular Events – Subject Level (Safety Population)

Parameter	ReSure Sealant (N=304) n (%)	Suture (N=183) n (%)	p-value[a]
Subjects with at least one AE	69 (22.7)	83 (45.4)	<0.0001
Subjects with most severe AE			
No AEs	235 (77.3)	100 (54.6)	<0.0001
Mild	60 (19.7)	75 (41.0)	
Moderate	7 (2.3)	7 (3.8)	
Severe	2 (0.7)	1 (0.5)	
Subjects with at least one serious AE	3 (1.0)	0 (0.0)	0.2949
Subjects with at least one AE related to study device[b]	5 (1.6)	56 (30.6)	<0.0001
Subjects with at least one AE related to cataract surgery[b]	53 (17.4)	63 (34.4)	<0.0001
Subjects with at least one Unanticipated Adverse Device Effect	0 (0.0)	0 (0.0)	----

[a]p-value based on the Mantel-Haenszel row mean scores test for Most Severe AE testing for a difference in means between treatments with scores assigned as follows: 0=No AEs, 1=Mild, 2=Moderate, and 3=Severe. P-value based on Fisher's Exact Test, testing for a difference in proportions between treatments for all other variables.

[b]AEs with an Unable to Determine relationship were excluded.

The most commonly reported adverse ocular events defined as occurring in 2 or more subjects are summarized in **Table 22**. There were no differences in the subject level event rates for most categories of AEs.

Table 22: Most Commonly Reported Adverse Ocular Events ≥ 2 Subjects – Subject Level (Safety Population)

Adverse Ocular Event	ReSure Sealant (N = 304)		Suture (N = 183)		p-value[a]
	n (%)	95% CI for %[b]	n (%)	95% CI for %[b]	
Anterior chamber cells greater than level 1+ persisting beyond Day 7 visit	4 (1.3)	(0.0036, 0.0333)	2 (1.1)	(0.0013, 0.0389)	1.0000
Corneal abrasion	1 (0.3)	(0.0001, 0.0182)	1 (0.5)	(0.0001, 0.0301)	1.0000
Corneal edema greater than level 1 persisting beyond Day 7 visit	1 (0.3)	(0.0001, 0.0182)	2 (1.1)	(0.0013, 0.0389)	0.5595
IOP > or = 30 mmHg or 10 mmHg over baseline	16 (5.3)	(0.0304, 0.0841)	15 (8.2)	(0.0466, 0.1316)	0.2499
Induced corneal astigmatism with a threshold of 3 diopters	9[c] (3.0)	(0.0136, 0.0555)	3 (1.6)	(0.0034, 0.0472)	0.5482
Posterior vitreous detachment	5 (1.6)	(0.0054, 0.0380)	1 (0.5)	(0.0001, 0.0301)	0.4173
Subconjunctival hemorrhage	1 (0.3)	(0.0001, 0.0182)	40 (21.9)	(0.1610, 0.2855)	<0.0001
Worsening in BCVA > 2 lines (>10 letters)	21 (6.9)	(0.0433, 0.1037)	9 (4.9)	(0.0227, 0.0913)	0.4400
Cystoid macular edema	0 (0.0)	(0.0000, 0.0121)	2 (1.1)	(0.0013, 0.0389)	0.1407
Eye irritation	0 (0.0)	(0.0000, 0.0121)	8 (4.4)	(0.0191, 0.0843)	0.0004
Eye pain	8 (2.6)	(0.0114, 0.0512)	7 (3.8)	(0.0155, 0.0772)	0.5893
Foreign body sensation	2 (0.7)	(0.0008, 0.0236)	7 (3.8)	(0.0155, 0.0772)	0.0301
Suture related complication	0 (0.0)	(0.0000, 0.0121)	2 (1.1)	(0.0013, 0.0389)	0.1407

Note: The denominator for the calculation of the percentage is N, the number of subjects in the treatment group, and the numerator is the number of subjects with at least one adverse ocular event of the given type.

[a]p-value is from Fisher's Exact Test, testing for a difference in proportions between treatments.

[b]Clopper-Pearson exact confidence interval for a binomial proportion.

[c]These ReSure Sealant subjects include: 1) one subject who received a suture intra-operatively subsequent to partial application of ReSure Sealant due to lack of a dry ocular surface, and 2) two subjects who had localized elevation changes consistent with having residual ReSure Sealant on the eye.

Table 23 summarizes several dichotomous safety outcomes by treatment group. There were no events reported in either treatment group for the first 2 categories of events; i.e., hypotony due to a wound leak or peripheral corneal edema affecting visual acuity. One (1) subject treated with ReSure Sealant (0.3%) required surgical intervention for management of a wound leak detected via positive Seidel test at Day 3 (details provided in **Section 5.3.2**).

The incidence of any major or serious adverse ocular events was very low and did not differ between the two groups 1.6% vs. 0.5% respectively (p=0.4173). These events included one event each of macular edema, non proliferative diabetic retinopathy with cystoid macular edema (CME), Descemet's membrane detachment, acute postoperative inflammation, and chronic iridocyclitis in the ReSure group and one event of CME in the Suture group. None of these events were determined to be related to the study device by the Investigator. Within this study, the incidences of post-surgical complications for both treatment

groups (captured as any major or serious adverse ocular event) were within the allowable thresholds noted in the "FDA grid" or within ISO 11979-7 (Ophthalmic implants – Intraocular lenses – Part 7: Clinical investigations Amendment 1).

Table 23: Additional Safety Outcomes (Subject Level) – Dichotomous Safety Events (Safety Population)

Variable	Statistic	ReSure Sealant (N=304)	Suture (N=183)	Difference in % (Suture - ReSure Sealant) and 95% CI[a]
Hypotony due to a wound leak	n/N (%)	0/304 (0.0)	0/183 (0.0)	0.0 (--, --)
	95% CI for %[b]	(0.0 , 1.2)	(0.0 , 2.0)	
Peripheral corneal edema affecting visual acuity	n/N (%)	0/304 (0.0)	0/183 (0.0)	0.0 (--, --)
	95% CI for %[b]	(0.0 , 1.2)	(0.0 , 2.0)	
Surgical reintervention for management of wound leak	n/N (%)	1/304 (0.3)	0/183 (0.0)	-0.3 (-1.0, 0.3)
	95% CI for %[b]	(0.0 , 1.8)	(0.0 , 2.0)	
	p-value[c]			1.0000
Any major* or serious adverse ocular event	n/N (%)	5/304 (1.6)	1/183 (0.5)	-1.1 (-2.9, 0.7)
	95% CI for %[b]	(0.5 , 3.8)	(0.0 , 3.0)	
	p-value[c]			0.4173

[a]Confidence interval based on the normal approximation.
[b]Clopper-Pearson exact confidence interval for a binomial proportion.
[c]p-value from a two-sided test for superiority based on Fisher's Exact Test, testing for a difference in proportions between treatments.
* Major adverse ocular events were classified based on the events included in the "FDA Grid" for historical adverse ocular event rates described in the draft FDA Guidance Document: Intraocular Lens Guidance Document. These events could include hyphema, macular edema, retinal detachment, pupillary block, lens dislocation, endophthalmitis, hypopyon, surgical reintervention, persistent macular edema, persistent corneal edema, persistent iritis, and persistent raised IOP requiring treatment, where a persistent adverse ocular event is defined as an adverse ocular event present one year post-operatively.

5.4.5 Serious Adverse Ocular Events

There were 3 SAEs for 3 subjects within the ReSure Sealant group. Brief narratives for each of the events are provided below. All 3 SAEs were considered unrelated to the study device and are consistent in nature and severity for a patient population undergoing cataract phacoemulsification and IOL placement. There were no SAEs in the Suture group.

SAE #1: Non Proliferative Diabetic Retinopathy with CME

Fifteen (15) days after cataract extraction a subject with a history of non-insulin dependent diabetes mellitus complained of visual disturbances and was found to have non-proliferative diabetic retinopathy with cystoid macular edema of the study eye. Focal laser photocoagulation was performed. Six days after the laser treatment the subject's tested visual acuity was logMAR 1.00. After completing the study through the Day 28 visit per protocol, the subject failed to keep additional follow-up appointments, but did return to the office approximately 3 months after cataract surgery. The subject had significantly improved. The subject had a measured Snellen best corrected visual acuity of 20/40 and was found to

have no CME. However, non-proliferative diabetic retinopathy is a chronic condition and is not expected to resolve, so the event was considered on-going. The Investigator considered this SAE as unrelated to the study device and unrelated to the study procedure, citing the subject's pre-existing condition of diabetes as the most likely cause. The Investigator noted that the subject had non-proliferative diabetic retinopathy with cystoid macular edema at baseline, but was unable to visualize it through the cataract.

SAE #2: CME Descemet's Membrane Detachment

On June 26, 2012, a subject underwent cataract surgery for the right eye. Seven days after cataract surgery the subject presented on the Day 7 visit complaining of blurring vision. The subject's measured best corrected visual acuity was logMAR 0.62 as compared to a best corrected visual acuity of logMAR 0.28 in the affected eye prior to cataract extraction and logMAR 0.30 at the Day 3 visit. The slit lamp examination revealed grade 0.5+ (1-5 cells) anterior chamber cells, grade 1+ (faint) flare, moderate levels of conjunctival erythema, and severe levels of stromal edema. ReSure Sealant was absent at this time and the subject had no presence of wound leak as confirmed by Seidel test. At the subject's Day 14, 21, and 28 visits, the Investigator noted continued severe corneal edema.

The subject was initially treated for toxic anterior segment syndrome. On August 24, 2012, the subject's corneal edema had slightly reduced allowing the Investigator to visualize Descemet's membrane which was found to be detached. The subject's Descemet's membrane was subsequently reattached via filling the anterior chamber with an air bubble. The subject returned on August 31, 2012 with a measured Snellen best corrected visual acuity of $20/50^{-2}$. The Descemet's membrane detachment was much smaller by size and affected surface and the gas was still present. There was no epithelial edema, stromal edema, anterior chamber cells or flare. On September 24, 2012, the subject returned to the office and had a Snellen BCVA of $20/40^{-2}$. The Descemet's membrane was fully attached with several folds at the level of Descemet's membrane. The subject was scheduled for a YAG Capsulotomy on November 7, 2012 to address a new finding of Posterior Capsular Opacity, and therefore the event was considered ongoing. The Investigator considered this SAE unrelated to the study device and related to the study procedure. In the Investigator's opinion, the Descemet's membrane detachment was caused by stromal wound hydration. Descemet's membrane detachment is a known, but rare complication of cataract extraction and IOL insertion.[31]

SAE #3: Acute Postoperative Inflammation

On August 7, 2012, a subject underwent cataract surgery for the right eye. ReSure Sealant was present over the incision at the Day 1 visit but not at the Day 3 visit. There was no presence of wound leak as confirmed via Seidel test at either visit. The subject returned for an unscheduled visit August 11, 2012, postoperative day 4, with acute postoperative inflammation and complaints of blurred vision and eye pain. The subject could only visualize hand movement. The slit lamp examination revealed mild levels of conjunctival erythema, conjunctival edema and a grade of 1+ (6-15) anterior chamber cells along with fibrin in the anterior chamber with no hypopyon. The Investigator took a conservative approach and treated the subject for presumed endophthalmitis and referred the subject to a retinal specialist. Two cultures of vitreous were negative with no growth. On September 5, 2012, the subject was seen again by the retinal specialist who noted resolution of the event. The subject was seen for the last time on November 1, 2012 by the Investigator. The subject's Snellen BCVA was measured to be $20/50^{+1}$. The

anterior chamber was noted to be deep and clear with no cells or flare. Examination indicated posterior synechiae to IOL, posterior vitreous detachment and fibrin membrane on IOL. The Investigator considered this SAE of acute post-operative inflammation unrelated to the study device and related to the study procedure. Acute postoperative inflammation is a known complication of cataract extraction and IOL insertion.

Clinical Perspective: *All 3 SAEs were considered unrelated to the study device and are consistent in nature and severity for a patient population undergoing cataract phacoemulsification and IOL placement.*

5.4.6 Masking Effectiveness

Results of the masking effectiveness assessment are provided in **Table 24**. In general it is very difficult to mask subjects within a device study, particularly when the nature of the study device, ReSure Sealant, is vastly different from the suture control. However, based on the fact that a significant proportion of subjects randomized to the Suture group believed they were treated with ReSure Sealant and there were a substantial proportion of responses of "unsure" within each treatment group (approximately a quarter to a third of the subjects in each group), the results indicate that efforts made to keep subjects masked from their treatment assignment were relatively effective. Therefore, in can be concluded that bias to patient rated outcome measures such as the Ocular Comfort Index was minimized.

Table 24: Masking Effectiveness Assessment

Variable	ReSure Sealant (N=305) n (%)	Suture (N=183) n (%)
Masking Effectiveness Assessment Response		
ReSure Sealant	194 (65.3)	72 (39.6)
Suture	32 (10.8)	46 (25.3)
Unsure	71 (23.9)	64 (35.2)

Clinical Perspective: *Measures taken to mask treatment assignment were relatively effective in that a large proportion of subjects in both treatment groups were either unsure of or guessed incorrectly concerning which treatment they received.*

5.4.7 Safety Conclusions

The following conclusions can be stated from the safety analyses:

1. The overall incidence of adverse ocular events reported for subjects treated with ReSure Sealant was significantly lower than for subjects treated with suture (22.7% vs. 45.4%, $p<0.0001$). This

difference in adverse ocular event rate between the two groups is attributed primarily to the higher incidence of device-related adverse events in the Suture group. Within the ReSure group the percentage of subjects experiencing device-related AEs was significantly lower than for the Suture group (1.6% vs. 30.6%, $p<0.0001$). Excluding the adverse ocular events for subjects in the Suture group that were device related or with "unable to determine" relationship (i.e., the events of subconjunctival hemorrhage, eye irritation, eye pain and others), there is no difference in between the ReSure group (22.7%) and Suture group (21.9%) for the remaining events (*post hoc* analysis; Fisher's Exact Test; $p=0.9107$).

2. Within both treatment groups, the majority of AEs were mild in severity. The percentages of subjects experiencing severe adverse ocular events were comparable between the two groups; 0.7% for the ReSure group and 0.5% for the Suture group. There were no severe device-related events or any unanticipated adverse device effects noted for either treatment group.

3. Three subjects (1.0%) treated in the ReSure group experienced an SAE including 1 event each of non-proliferative diabetic retinopathy with CME, Descemet's membrane detachment and acute post-operative inflammation. None of these 3 serious adverse ocular events were determined by the Investigator to be device-related but 2 were determined to be procedure related as they are recognized complications associated with cataract surgery. The nature of these serious adverse ocular events reported is consistent with a patient population undergoing phacoemulsification for cataract extraction with IOL placement. In both treatment groups the rates of adverse ocular events addressed in either the "FDA grid" or ISO 11979-7 "Ophthalmic implants – Intraocular lenses – Part 7: Clinical Investigations Amendment 1" for subjects undergoing posterior chamber IOL placement were within the threshold rates cited in these documents.

4. There were no statistically significant differences between the two groups for the incidence of corneal edema (moderate to severe stromal edema) at Day 1 or $\geq$ grade 2+ anterior chamber inflammation at Day 1 (endpoints that had been established *a priori* for potential inclusion in the product labeling).

In summary, the safety assessments performed per protocol throughout the follow-up period did not raise any safety concerns and provide evidence that ReSure Sealant is well tolerated by the human eye. No safety issues were identified by the investigative sites, Sponsor, or Medical Monitor. There are no adverse events related to ReSure Sealant that are ongoing. All device-related events were resolved without any residual effects or lasting sequelae. ReSure Sealant has been demonstrated to have a favorable safety profile for application to human ocular tissues.

6.0 RISK-BENEFIT ASSESSMENT

6.1 Risks of ReSure Sealant

Within the ReSure Sealant Pivotal Study, safety of the subject device was assessed via evaluation of spontaneously reported adverse ocular events and through a multitude of specific ocular assessments including but not limited to evaluation of BCVA, slit lamp biomicroscopy, intraocular pressure measurements, wound healing and the OCI questionnaire. Overall, among the assessments performed there were no indications that the ReSure Sealant presented a risk over and above that of cataract surgery alone.

The overall incidence of adverse ocular events reported for subjects treated with ReSure Sealant was significantly lower than for subjects treated with suture (22.7% vs. 45.4%, $p<0.0001$) and, in particular, the rate of device-related adverse events was substantially higher in the Suture treatment group (1.6% vs. 30.6%, $p<0.0001$). The incidence of subconjuctival hemorrhage (0.3% vs 21.9%, $p<0.0001$), eye irritation (0.0% vs. 4.4%, $p=0.0004$) and foreign body sensation (0.7% vs. 3.8%; $p=0.0301$) were all significantly greater for subjects treated with sutures. ReSure Sealant provided for a better safety profile than sutures while at the same time demonstrating superior effectiveness in the treatment of incisional leaks.

Excluding the adverse ocular events within the Suture group that were either device related or with "unable to determine" relationship (i.e., the events of subconjunctival hemorrhage, irritation, eye pain and others), there is no difference in between the ReSure group (22.7%) and Suture group (21.9%) for the remaining events (*post hoc* analysis; Fisher's Exact Test; $p=0.9107$). This latter comparison provides strong evidence that the nature and incidence of adverse ocular events observed in the ReSure Sealant group is consistent with a patient population undergoing phacoemulsification for cataract extraction with IOL placement and that ReSure Sealant presents no risk over and above that of cataract surgery alone.

Three (3) subjects (1.0%) treated in the ReSure group each experienced a single SAE: one each of non-proliferative diabetic retinopathy with cystoid macular edema, Descemet's membrane detachment and acute post-operative inflammation. None of the serious adverse ocular events were determined to be device-related and all were within the threshold rates cited within the "FDA grid" for historical adverse event rates included in the draft FDA Guidance Document: Intraocular Lens Guidance Document.

Through risk analysis activities performed in compliance with Quality System design controls, several theoretical risks have been identified that may be potentially associated with the use of ReSure Sealant. Potential risks identified in risk assessment activities, relevant observations from the ReSure Sealant Pivotal Study, and risk mitigation activities that have been undertaken to minimize the specific risks are described in **Table 25**.

Table 25: Potential Risks and Associated Risk Mitigation Measures

Potential Risk	Relevant Findings from the ReSure Sealant Pivotal Study	Risk Mitigation Measures
Eye Irritation	There were no adverse events of eye irritation in the ReSure Sealant group vs. 4.4% in the Suture Group.	Material selection: the materials of manufacture have been selected for their long-term application in ophthalmic applications. Preclinical evaluations have established that ReSure Sealant is a non-irritant to ocular tissues.
Discomfort/Pain	The incidence of eye pain as an adverse event was low at 2.6% for ReSure treated eyes vs. 3.8% in the suture control group. Additionally, Ocular Comfort Index (OCI) scores were similar between treatment groups at baseline and all post-surgical time points with no clinically relevant differences evident.	Material formulation: Hydrogel has been formulated to be soft, lubricious, tissue conforming and minimize material swelling. The modulus of elasticity is similar to tissue. It is chemically engineered to provide acute coverage until the wound is epithelialized.
Ocular Trauma due to Applicator	Corneal abrasion occurred in 1 subject each in the ReSure Sealant and Suture groups for an incidence of 0.3% and 0.5% respectively (p=1.0000). The one incidence of corneal abrasion within the ReSure group occurred 1 day after the procedure and was deemed not to be device-related. The abrasion was treated with systane and resolved with no residual effects by the time the subject returned for the Day 14 visit. Based on the results of the study the applicator and application of ReSure Sealant does not appear to invoke ocular trauma.	Applicator has been designed to provide an atraumatic (soft) tip (no sharp edges, and flexible to minimize forces applied to ocular tissue). Instructions for use provide appropriate instructions for applicator use.
Inflammation/ Allergic reaction	Sit lamp exam findings were consistent with the normal post-operative course for a population undergoing cataract surgery, with early findings of primarily mild postoperative inflammation which decreased over time. One eye treated with ReSure Sealant experienced an SAE of acute post-operative inflammation which was treated with prophylactic antibiotics (no evidence of infection) and steroids. Due to the course of the adverse event, this SAE was assigned by the Investigator as unrelated to the study device and related to the study procedure. The findings indicate that ReSure Sealant is well tolerated and does not promote corneal or anterior chamber inflammation.	Material formulation: ReSure has been designed/ formulated with constituents with a known history of safe use in medical devices and ophthalmic devices in particular. Full biocompatibility testing in compliance with ISO 10993 including ocular and intraocular toxicity studies were performed with passing results for all studies.

Potential Risk	Relevant Findings from the ReSure Sealant Pivotal Study	Risk Mitigation Measures
Visual Impairment	BCVA scores and change from baseline scores were similar between treatment groups at baseline and all post-surgical time points. Additionally, there was no difference in the incidence of BCVA worse than 20/40 on the final study visit at Day 28 between the ReSure group and Suture group, 3.3% and 3.9%. The proportion of eyes with BCVA worse than 20/40 observed for both treatment groups within the study is consistent with that reported in the early follow-up in anterior chamber intraocular lens PMA studies.	Material selection: ReSure has been designed/ formulated with constituents with a known history of safe use in medical devices and ophthalmic devices in particular. Full biocompatibility testing in compliance with ISO 10993 including ocular and intraocular toxicity studies with passing results for all studies performed. Material is translucent and is applied outside of the visual axis.
Delayed Healing	There were no epithelial defects in ReSure treated eyes at the Day 7 and Day 28 visits. One ReSure treated eye had wound healing characterized as outside normal limits due to the presence of mild stromal edema which did not meet the definition of an adverse ocular event. This subject had experienced an ocular adverse event of corneal edema greater than level 1 persisting beyond the Day 7 visit that improved to grade 1 by the Day 21 visit but continued to be treated with topical Pred Forte and Muro 128 topical ophthalmic ointments at and beyond the Day 28 visit (due to persistent mild corneal edema). No additional abnormal slit lamp findings were noted for this subject.	Material selection and proper instructions to assure material is not pressed into incision**.**
Infection	There were no incidences of infection in ReSure or Suture treated eyes.	Appropriate packaging and sterilization validation activities have been undertaken to assure product sterility. Also instructions for use provide information to assure proper application technique using aseptic protocols**.**

6.2 Benefits of ReSure Sealant

Compared with scleral incisions, CCIs, by their nature, are less forgiving and more difficult to construct properly even by an experienced surgeon[32] and due their avascular nature are slower to heal.[33] Moreover, occupancy of the wound can impede the hermetic closure of the incision. It can be caused by autologous organic tissues such as epithelium, iris, vitreous, lens, capsule, lens masses, or by foreign bodies such as eyelash fragments, threads, cloth filaments, and surgical detriti.[34]

In a study performed by Wallin. *et al*. which compared patients with post-cataract surgery bacterial endophthalmitis to control patients who underwent cataract surgery without an event of endophthalmitis, wound leak on the first postoperative day (whether a microleak or gross leak) was a significant risk factor for infection (odds ratio 44 ± 42; $p<.001$).[35] In addition to infections, wound leaks can be a causative

factor for hypotony, corneal decompensation, epithelial down growth and fistulization, which are all potential sight-threatening events. [34,36,37] In the 488 subjects evaluated in the ReSure Sealant Pivotal Study, all subjects received incision closure either by suture or ReSure Sealant and none of the subjects experienced these complications suggesting proper sealing prevents or reduces their occurrence. Although these events are rare, due to the serious nature of these complications it is imperative that the clear corneal incision is properly sealed at the end of surgery.

If wound integrity is suspect, the only current treatment option for definitive closure is sutures. Although stromal hydration is frequently used, the stability of incisions treated with stromal hydration has been come into question based on reports of epithelial gaping[3,10] and leak rates of 50-85% in the immediately post-operative period.[8,11,12] Sutures are considered the current gold standard for ensuring closure of CCIs, but they are not ideal. Sutures can result in poorly apposed wounds,[13] can cause tissue damage, and histological imaging has demonstrated they can cause vacuole formation in the corneal epithelium.[14] Sutures provide a relatively weak resistance to wound leakage, similar to fibrin adhesives;[23] 23.8% of sutured CCIs showed leakage after application of one ounce force.[12] Studies comparing sutureless and sutured CCIs have produced conflicting results with regard to their overall effect; different India ink inflow patterns have been observed in different studies.[7,13] It is recommended that sutures be removed promptly once healing is complete to decrease the chances of infection.[15,16] This requires additional post-operative visits, which may be inconvenient for the patient and time-consuming for the surgeon.

Although sutures are currently the most effective option for closing clear corneal incisions, there is often a reluctance to use a suture due to the concerns that suture complications may ensue. For this reason, ReSure Sealant represents a novel technology that currently addresses an unmet medical need; i.e., an alternative to sutures for definitive wound closure. Relative to sutures, ReSure Sealant is easy to apply and provides definitive closure without invoking additional defects (i.e., needle holes) in the corneal epithelium. Additionally, since ReSure Sealant is only present on the eye only during the first few post-operative days during the period of epithelial healing, after which it sloughs off, a secondary procedure for removal is not required. Indeed, within the ReSure Sealant Pivotal Study, ReSure Sealant was found to be more effective than suture for treatment of intraoperative wound leaks and was associated with fewer device-related adverse events and an overall adverse event rate that was significantly lower than that observed with sutures.

6.3 Risk-Benefit Summary

The results from ReSure Sealant Pivotal Study have demonstrated that the device is a safe and effective option for cataract patients. Compared with sutures, application of ReSure Sealant eliminates the need for a secondary procedure (i.e., suture removal) and was shown to be more effective than suture at preventing wound leaks while associated with significantly fewer device-related adverse events. Risks have been mitigated through standard risk mitigation activities including proper design and material formulation, preclinical safety studies and clear instructions in the labeling regarding the safe and effective use of the device. In summary, the benefits presented by the application of ReSure Sealant outweigh the potential risks. The clinical advantages provided by ReSure Sealant make the device a desirable addition to the refractive cataract surgical armamentarium.

Clinical Perspective: *ReSure Sealant demonstrated superior effectiveness to sutures in the treatment of incisional leaks while at the same time providing a better safety profile.*

7.0 OVERALL CONCLUSIONS

Based on the data presented within this document, the safety and effectiveness of ReSure Sealant has been established. ReSure Sealant was demonstrated to be superior to suture, the current gold-standard for closing clear corneal cataract incisions and preventing incisional leaks. Additionally, ReSure Sealant was associated with fewer device-related adverse events and an overall adverse event rate that was significantly lower than that observed with sutures. Results from the ReSure Sealant Pivotal Study clearly provide objective scientific evidence that ReSure Sealant is safe and effective for use for the intraoperative management of clear corneal incisions with a wound leak demonstrated by Seidel test, and for prevention of postoperative fluid egress following cataract or intraocular lens placement surgery, and therefore, is a valuable alternative surgical tool to sutures for providing safe and effective closure of a clear corneal incision.

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